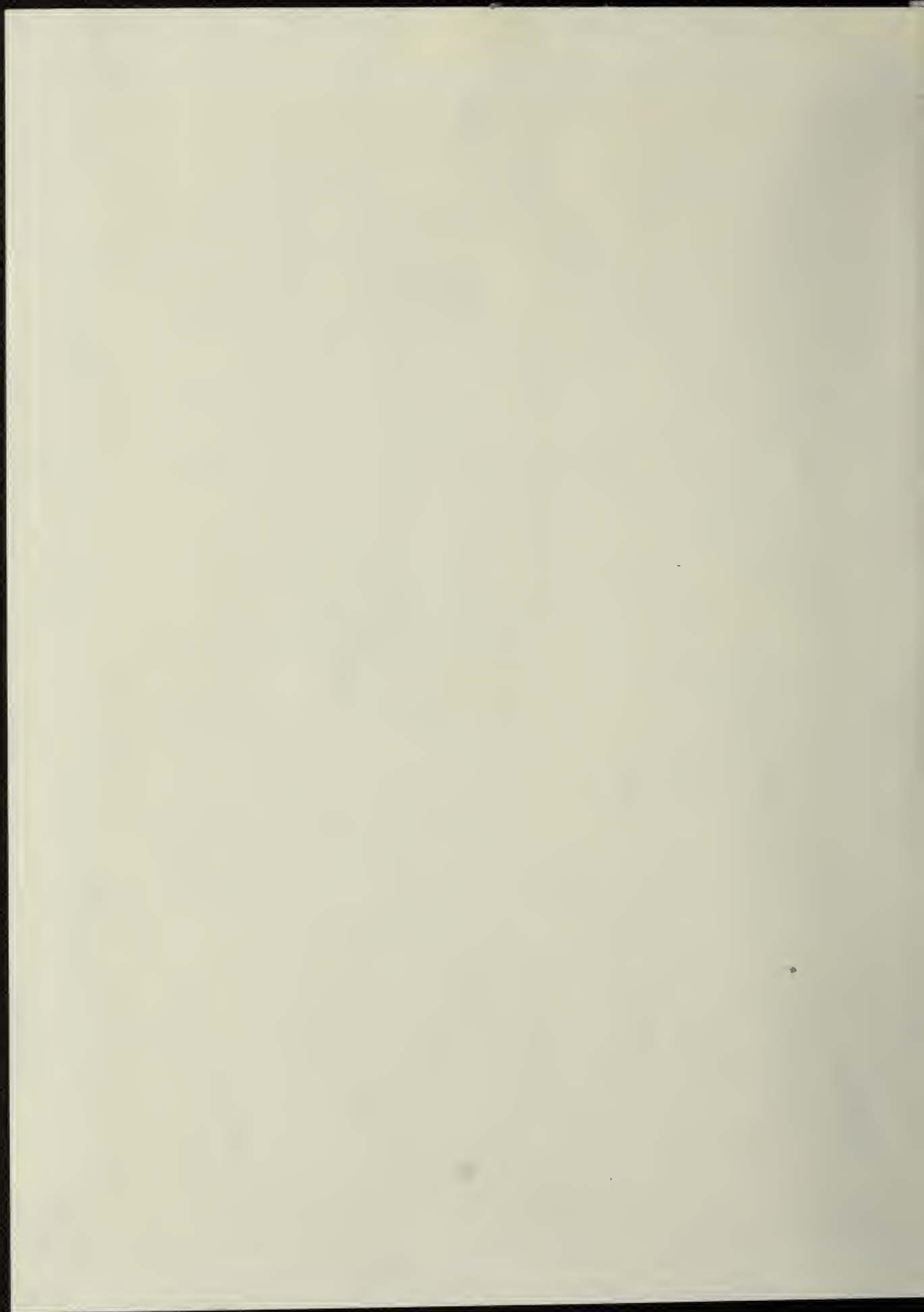


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CARCINOGENESIS ABSTRACTS

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CARCINOGENESIS ABSTRACTS

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CARCINOGENESIS ABSTRACTS makes available abstracts, annotations or citations of significant carcinogenesis articles collected from the current major biomedical sources of world literature. This service is provided by the National Cancer Institute through a contract with the Franklin Research Center for preparation of the publication, under Contract No. NOI-CP-75885 with the National Cancer Institute, U.S. Department of Health, Education and Welfare. Published and distributed by the Franklin Institute PressSM.

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ABBREVIATIONS

JOURNAL names are abbreviated according to the *List of Journals Indexed in Index Medicus, Abbreviation Listing*. If the journal is not listed in this, abbreviations are derived from the *International List of Periodical Title Word Abbreviations*.

LANGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

ABBREVIATIONS used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μl	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μCi	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED₅₀	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO₂	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μg	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intra-dermal	SGOT	serum glutamic-oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT	serum glutamic-pyruvic transaminase
IgB	Immunoglobulin B	soln	solution
IgG	Immunoglobulin G	TCD	tissue culture dose
IgM	Immunoglobulin M	TCD₅₀	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intraperitoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
K_m	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD₅₀	median lethal dose		
M	molar		
μM	micromolar		



REVIEW

79-0001 Decision Point Approach to Carcinogen Testing. (Eng) Weisburger, J. H. (American Health Foundation, Valhalla, NY, 10595); Williams, G. M. In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977.* Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 45-52; 1978.

A standardized approach to assessing potential human cancer risk, the Decision Point Approach, consists of a sequential series of tests and a final evaluation. The first area of concentration should be structure-activity correlations. Studies of compounds such as azo dyes and arylamines reveal that data on the structure of the suspect chemical as well as potential metabolites can lead to success in predicting the carcinogenicity of untested structurally related compounds. A series of rapid in vitro tests (applied as a battery) should follow. They comprise mutagenicity, DNA repair, and cell transformation tests. The next steps are a series of limited bioassays in rodents and conventional chronic toxicity and carcinogenicity tests. The decision as to whether a material is a cancer risk is made after a two-stage review. First, a body of cancer experts would review the data to decide if a carcinogenic risk may be present; a negative decision would solve the question. A positive vote would be passed on to a board comprised of many representatives of society, who would weigh risks vs benefits and make a recommendation as to the use of the material. (62 refs)

79-0002 Models for Carcinogenic Risk Assessment (6 Letters to Editor). (Eng) Brown, C. C. (NCI, Bethesda, MD, 20014); Fears, T. R.; Gail, M. H.; Schneiderman, M. A.; Tarone, R. E.; Mantel, N.; McGaughey, C.; Crump, K. S.; Neyman, J.; Scherer, E.; Emmelot, P.; Cornfield, J. *Science* 202(4372): 1105-1109; 1978.

Five critiques and a rebuttal by the author are presented to a report of a simple kinetic model for carcinogenesis that could lead to a threshold. This threshold depends on the existence of at least one irreversible, completely protective reaction in carcinogenesis. Inadequacies in the derivation of the model are pointed out, and concern is expressed over the assessment of low-exposure carcinogenic risk. Deactivation of a toxic substance will take time to reach equilibrium and, under the assumption of proportionality between dose and the probability of a carcinogenic response, if any activated complex ever reaches the target site, a threshold will not exist. The model also unrealistically assumes that there is a single exposure in environmental carcinogenesis. In another cri-

tique, it is stated that the model does not account for initiation and promotion and thus has limited value when the possible combinations of initiating agents, promoting agents, and time frames are considered. The threshold model is unstable, since a slight perturbation of the model in the direction of realism does away with the threshold and leads to low-dose linearity. The model does not recognize that the response to a carcinogen depends on the rate of exposure and it does not allow for the phenomenon of synergism. According to another critique, the threshold holds for the special case of a steady-state model in which the deactivation reaction is irreversible and will not hold when the time course of the reaction is taken into account. The author answers that the model is not dependent on the existence of a threshold. (25 refs)

79-0003 Cancer Epidemiology--Part V. (Eng) Harberg, J. (Wisconsin Clinical Cancer Center, 1900 University Ave., Madison, WI, 53705); Buchanan-Davidson, D. *J. Wis Med J* 77(11): 26-27; 1978.

Risk factors and incidence and mortality patterns associated with stomach and colorectal cancer are presented from a review of the literature. Substances in the diet may be significant to both cancer types. (31 refs)

79-0004 Approaches to the Prediction of Carcinogenic Effects Using Quantitative Structure-Activity Relationships (QSAR). (Eng) Chu, K. C. (NCI, Bethesda, MD, 20014). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977.* Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 95-97; 1978.

In attempts to analyze the metabolic activation of chemicals, quantum mechanical (computer) studies are using models to predict the formation of ultimate carcinogens and also the criteria for their formation. The predictions are based on quantitative structure-activity relationships that are used in "fundamental" approaches to the mechanisms of carcinogenesis and in "empirical" approaches involving the analysis of existing data relating substructure to the biological response of previously tested compounds. Specifically, the fundamental approach examines how a compound might react with macromolecules (free radical, SN1, or SN2 type reactions), whereas the empirical approach examines the sum of parameters such as resonance, field and steric properties, and

lipophilic and conformational effects. In a general scheme of chemical carcinogenesis, a compound enters the body through the mouth, nose, or skin, and is absorbed into organs capable of metabolic activation. The chemical may then be eliminated, detoxified to inactive metabolites, or activated into a procarcinogen. The latter may, in turn, be activated to any ultimate carcinogen capable of binding covalently to macromolecules. If such conjugates affect macromolecule replication or its effect is not "repaired" by the cell, cancer induction will occur. (15 refs)

- 79-0005 Hansch Analysis and the Use of Partition Coefficients.** (Eng) Leo, A. J. (Pomona Coll., Ontario, CA, 91511). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977.* Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 55-62; 1978.

Hansch analysis is an extension of the Hammett equation of physical organic chemistry applied to bio- and medicinal chemistry. Drug transport is one of the most important phenomena of biosystems. Used in a linear fashion, the hydrophobicity parameter (partition coefficient) could not account for the fact that in some transport phenomena, an optimal hydrophobicity is apparent. In Hansch analysis, this might be explained in a kinetic model in which a series of lipid/aqueous compartments has to be traversed by the drug, with partitioning occurring between each phase boundary. Computer simulation readily shows that the rate at which the drug appears in the final compartment is a parabolic function of the partition coefficient. The hydrophobicity parameter should play an important role in assessing the danger of carcinogens to humans. The octanol-water partition coefficient can be a useful parameter to model the adsorption of chemicals to soil and their absorption into aerosols. Furthermore, partition coefficients have been conclusively shown to be an excellent parameter for modeling bioaccumulation. Hydrophobicity must always be taken into account in the design of experimental tests for carcinogenicity, as administration vehicles may affect the sensitivity of a test or the locus of primary tumors. (15 refs)

- 79-0006 Session II. Carcinogen Screening: Obstacles and Options. In Vitro Testing of Environmental Mutagens/Carcinogens.** (Eng) Ames, B. N. (Univ. California, Berkeley, CA, 94720). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977.* Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 27-33; 1978.

The development, accuracy, and recent applications of the Ames *Salmonella* mutagenesis test are discussed. Chemicals tested for mutagenicity and carcinogenicity have included flame retardants in children's pajamas, pesticides, vinyl chloride, and dibromo compounds in citrus-flavored soft drinks. (9 refs)

- 79-0007 In Vivo Testing of Carcinogens.** (Eng) Griesemer, R. A. (NCI, Bethesda, MD, 20014). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977.* Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 34-37; 1978.

Design considerations in in vivo carcinogen testing and obstacles to properly carrying out such tests are reviewed. In the approach used by the National Cancer Institute to identify chemical carcinogens, two species of animals of both sexes are exposed to the test chemical using the highest doses the animals can tolerate. After 2 yr, survivors are killed and the tumors produced compared with spontaneously occurring tumors in controls. The purity of the chemical and the nature and amount of any impurities must be known. The chances of detecting carcinogenicity are greatly enhanced when testing is conducted in several species of animals. The outcome may also be altered by the route of exposure and dosage. In many studies, the results are difficult to evaluate, especially in the case of benign tumors. It is necessary to distinguish between truly benign tumors and those lesions that are premalignant or potentially malignant; the distinction is not always possible. These tests only attempt to divide chemicals into carcinogens and noncarcinogens. Considerably more research related to risk assessment is necessary to provide a basis for regulatory action. (2 refs)

- 79-0008 Structure-Activity Studies of Chemical Carcinogens Using Quantum Chemical Methods.** (Eng) Loew, G. H. (Stanford Univ. Medical Center, Stanford, CA); Pack, G. R. In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977.* Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 197-199; 1978.

The use of quantum chemical methods to calculate molecular descriptors that have a meaningful relationship to carcinogenic potencies is discussed. Current knowledge of the steps leading to chemical carcinogenesis permits a classification into chemical families, whose individual members follow the same general pathways. The electronic structures and electrophilic reactivity of candidate ultimate carcinogens can be cal-

culated and used to test the electrophilic hypothesis of ultimate carcinogens. (9 refs)

- 79-0009 A Computerized Toxicity Estimation System.** (Eng) Enslein, K. (Genesee Computer Center, Rochester, NY, 14605). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977.* Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 82-87; 1978.

A computerized toxicity estimation system is presented and discussed. The proposed toxicity estimation model begins with 549 compounds from the 1974 "Toxic Substances List". These compounds are assigned partition coefficients and substructure codes that are fed into the computer data base. The modeled dependent variable is the "Rat Oral LD-50". Subpopulations are then generated by clustering and discriminant analysis. Two groups, high toxicity compounds and lower toxicity compounds, are finally analyzed through the derivation of regression equations. Discriminant analysis revealed a group of 31 compounds that did not fit into the larger group pattern. These were the most highly toxic compounds; and a discriminant equation was set up utilizing the 134 most often used fragments, mol wt, partition coefficient data, and various other interactions with a final set of 12 terms demonstrating significant predictive value. Results of regression analysis revealed the most important predictive parameter to be mol wt. Although Rat Oral LD-50 was used as the endpoint of this analysis, it is suggested that carcinogenesis applications of this method would follow similar lines. (2 refs)

- 79-0010 Carcinogen Binding to DNA.** (Eng) Neidle, S. (Dept. Biophysics, King's Coll., London, England). *Nature* 276(5687): 444-445; 1978.

The latest information on the interaction of a chemical carcinogen and its target molecule is reviewed. Polycyclic aromatic hydrocarbons are not directly carcinogenic but are metabolized in vivo to short-lived reactive species that bind to cellular macromolecules. Most evidence indicates that DNA is the critical receptor, but why the interactions of the reactive species with DNA are carcinogenic remains unknown. An important metabolite of benzo(a)pyrene is its 7,8-diol-9,10-epoxide, which binds predominantly to guanine residues in DNA, mainly at the N2 or N7 position. Circular dichroism spectroscopy showed that the BP diol epoxide was bound to the dinucleoside phosphate GpU at the N2 position of the guanine base. This interaction profoundly altered the conformation of the molecule around the guanine-sugar linkage, such that if it were in a double strand, the guanine would be forced out of its base-pairing position.

Several aromatic electrophilic carcinogens were analyzed for their ability to unwind closed, circular, supercoiled simian virus 40 DNA. Almost all compounds produced unwinding, although striking differences were noted among individual compounds. Unwinding ability was strongly correlated with frameshift mutagenic activity in a *Salmonella* Ames test. Thus, local unwinding of DNA is probably the consequence of the covalent binding of an active compound. This information was used to construct a plausible molecular model for the structure of the DNA adduct. In similar unwinding experiments, analyses of the S₁ nuclease-treated product showed that predominantly adenine residues were modified to cause local unwinding-induced denaturation, even though the guanine residues were the major sites for actual binding of carcinogen. It is suggested that there are at least two categories of base modification: adenine involvement, producing local unwinding and base-pair cleavage, and guanine attachment, with a less-drastic result. (no refs)

- 79-0011 Various Parameters Associated with Mutagenesis.** (Eng) Clive, D. (Burroughs Wellcome Co., Research Triangle Park, NC). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977.* Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 22-26; 1978.

The advantages and disadvantages of various mutagenicity assay systems are considered. Most mutagenicity measurements have been made in bacteria, but bacteria may not be the best basis for predicting mutagenicity and carcinogenicity in humans. Studies involving x-ray- and ethyl methanesulfonate-induced mutations in organisms of various sizes indicate that the sensitivity of a gene to a mutagen may depend on the type of organism bearing the gene and, in particular, on the size of the genome surrounding the target gene. The target size of the gene grows with the complexity of the organism carrying that gene. Of the various mutagenicity assay systems available (mouse specific-locus test, mammalian dominant lethal assay, insect assays, mouse recessive lethal assay, bacterial assays, and cultured mammalian cells), cultured mammalian cells may represent the best system for predicting effects in humans. This assay is inexpensive, fast, sensitive, can use large numbers of cells, can be used with exogenous mammalian metabolism, and can detect both gene and chromosomal mutations. Its disadvantages included the facts that exogenous metabolism may not be the same as in vivo metabolism and that it measures mutagenic potential only and not actual in vivo mutagenesis. (10 refs)

- 79-0012 Regulatory Considerations Concerning Mutagenesis.** (Eng) Kolbye, A. C. (Bureau Foods, Food and Drug Admin., Washington, DC, 20204). *J Soc Cosmet Chem* 29(11): 727-732; 1978.

The usefulness of the available mutagenesis test systems as a basis for regulatory decision-making is considered from the point of view of the Food and Drug Administration (FDA). The Ames mutagenesis test has many attractive features, including the ability to assess the mutagenic potency of a substance quantitatively over a very wide range of dosage. The Ames test is sensitive enough to detect the majority of chemical carcinogens presently identified as such, except for hormones, metals, and carcinogens dependent on physicochemical effects. It is fairly specific for the substances tested in that mutagenic effects have been detected for many carcinogens. However, the question of false-positive results has not been resolved yet and will only be settled by expanding the number of chemicals tested. Although the Ames test can quantitatively measure mutagenic strength over an exceedingly broad range of dosage, it does not measure penetrability of the substance in the intact animal or selective parameters such as biological resistance. It is recommended that more effort be devoted to expanding the number of substances tested to gain more insight into the specificity of the system to detect mutagenic carcinogens. Premature regulatory decisions may create unanticipated controversies. (5 refs)

- 79-0013 Environmental Mutagens and Carcinogens.**
(Eng) Nagao, M. (Nat'l. Cancer Center Res. Inst., Chuo-ku, Tokyo 104, Japan); Sugimura, T.; Matsu-shima, T. *Annu Rev Genet* 12(1): 117-159; 1978.

Various types of environmental mutagens are reviewed, and other factors related to the detection and study of these substances are discussed. Mutation tests using microbes, an in vitro transformation test using cultured mammalian cells, other short-term test systems for the detection of environmental mutagens and carcinogens, and in vivo long-term animal tests for environmental carcinogens are described. Naturally occurring agents include those produced by fungi and plants and fatty acid peroxides in foods. Among those produced by fungi, aflatoxin B₁ is the strongest mutagen and carcinogen. Proven or possible mutagens and/or carcinogens produced by other plants include cycasin, substance(s) in bracken fern, pyrrolizidine alkaloids, flavonoids, quercetin, hydrazine, safrole, isosafrole, dihydrosafrole, monocrotalin, and heliotrine. The fatty acid peroxide, malonaldehyde, has been found to be mutagenic to *Salmonella typhimurium* TA1978. Another source of environmental mutagens is pyrolysis products, which include cooking products, tobacco tar, and aromatic hydrocarbons. Other sources discussed include nitrosation products, synthetic chemicals (food additives, cosmetics, drugs, pesticides, household materials, and occupational substances and industrial intermediates), and water pollutants and air pollutants. In addition, factors modifying mutagenesis and carcinogenesis, evaluation and quantitation of data, and overlapping of mutagens and carcinogens are discussed. (311 refs)

- 79-0014 The Importance of Metabolic Considerations.**
(Eng) Clayson, D. B. (Eppley Inst., Omaha, NB,

68105). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977.* Office of Science, FDA Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 38-44; 1978.

The first two phases of carcinogenesis, the metabolic activation of procarcinogens and the interaction of the resulting electrophile with cellular macromolecules (DNA, RNA, and protein) are surveyed. Conversion into electrophiles is accepted as the key to the metabolic activation of most major classes of environmental carcinogens, including polycyclic aromatic hydrocarbons, alkylating agents, nitrosamides, nitrosamines, and aflatoxins. Concerning electrophile-DNA binding, infidelity in DNA replication has been shown to be induced by 0-6 but not N-7 methylation of guanine. The realization that carcinogens need metabolic activation and that the success of the *Salmonella* and other microbial tests depends not only on the use of suitable test bacteria but also on the addition of metabolic enzymes or microsomes (plus necessary cofactors) to the system increased the parallelism between mutagenicity and carcinogenicity test results. In vivo metabolic assays, nonspecific agents can modify metabolism and thus the proportion of a procarcinogen dose that is converted to an ultimate carcinogen. These agents include enzyme inducers, specific enzyme cofactors, enzyme poisons, antioxidants, hormones, and compounds that affect the nutritional status of the test animals. (24 refs)

- 79-0015 Carcinogenic Risk Estimation for Chloroform: An Alternative to EPA's Procedures (Letter to Editor).** (Eng) Reitz, R. H. (Toxicology Res. Lab., Dow Chemical Co., 1803 Building, Midland, MI, 48640); Gehring, P. J.; Park, C. N. *Food Cosmet Toxicol* 16(5): 511-514; 1978.

A discussion is presented that evaluates the overestimation of the magnitude of the cancer risk from chloroform as estimated by the Environmental Protection Agency (EPA) from data generated at NCI. There are two reasons why this particular risk extrapolation is probably inaccurate. First, the EPA has failed to consider important data concerning the mechanisms through which chloroform exerts its toxicity. The mathematical model used by the EPA for species/species extrapolation assumes direct cytotoxicity of the chemical in question. However, the toxicity of chloroform is apparently due not to the parent molecule itself, but rather to the production of reactive metabolites that bind covalently to tissue proteins. This difference has led to a major error in extrapolating from laboratory rodents to man. Secondly, the NCI study was carried out with very high doses of chloroform. However, there is evidence of a sudden change in the shape of the dose-response curve of chloroform when the dose falls below 200 mg/kg, resulting in a sharp decrease in oncogenicity. This latter finding suggests that there may be detoxification mechanisms that effectively protect the animals until they are overwhelmed by very large doses. In view of the fact that the

EPA has, on the basis of the NCI study, proposed an amendment to the Safe Drinking Water Act establishing a Maximum Contaminant Level of 0.1 ppm of chloroform, it is suggested that the risk estimation be performed as accurately as possible so that the risk/benefit ratio may be properly considered. (no refs)

- 79-0016 Trichloroethylene: Hepatic Effects, Metabolism and Elimination.** (Eng) Cooper, P. (No affiliation given). *Food Cosmet Toxicol* 16(5): 491-492; 1978.

Studies concerning the metabolism, elimination, and hepatic effects of trichloroethylene (TCE) are reviewed. These include investigations of the relationship between the degree of exposure and the excretion of the solvent and its metabolites, and the relationship between the hepatotoxicity of TCE and its metabolism. Metabolites formed during the microsomal metabolism of TCE and impurities and additives contained in technical grade TCE are also discussed. (11 refs)

- 79-0017 Carcinogenicity of Esters and Benzylic Alcohols.** (Eng) Poirier, L. (NCI, Bethesda, MD, 20014); Helmes, C. T. In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977*. Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 179-183; 1978.

A review of the structure-activity relationships of carcinogenic and noncarcinogenic esters indicated that the carcinogenic activity of carboxylic esters (CE's) is independent of the structure of the acid portion of the molecule. CE's whose alcohol portion is extensively stabilized by resonance or induction are likely to be carcinogenic, but CE's whose potential carbonium ion is minimally stabilized by resonance or induction are unlikely to be carcinogenic. These generalizations apply only to CE's since carboxylate ion is a weak leaving group. However, stabilization of the ensuing carbonium ion is helpful in carcinogenesis. Investigation of the carcinogenic potential of benzylic alcohols has failed to reveal a structure-activity relationship for carcinogenesis, although there is suggestive evidence that benzylic alcohol formation is a potential major route of carcinogen activation. (15 refs)

- 79-0018 Structural Parameters Associated with Carcinogenesis (Halogenated Olefins, Vinyl and Allyl Analogs and Epoxides).** (Eng) Fishbein, L. (Nat'l. Center Toxicological Res., Little Rock, AR, 72207). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in*

Annapolis, 31 August-2 September 1977. Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 8-21; 1978.

A number of reportedly carcinogenic industrial compounds (including halogenated olefins, vinyl and allyl analogs, and epoxides) were examined to determine if their structural, biological, and metabolic similarities could help predict their carcinogenicity. The chlorinated olefinic derivatives of major concern are vinyl chloride, vinylidene chloride, trichloroethylene, chloroprene, dichlorobutene, and perchloroethylene, all of which have been proved to be carcinogenic to humans and/or laboratory animals. Evidence suggests that all chlorinated ethylenes are metabolized to oxiranes (epoxides) as a first step. The oxiranes, which are strongly electrophilic, may react directly with cell nucleophiles or they may undergo intramolecular arrangements. No such structure-activity relationship has been demonstrated for the various vinyl and allyl analogs that are carcinogenic and/or mutagenic. In the case of the epoxides, the presence of a reactive functional group (as in epichlorohydrin) or a double bond (as in glycidaldehyde) near the epoxide appears to enhance carcinogenicity by allowing the chemical to act as a difunctional alkylating agent for macromolecules. Greater reliance should be placed on mutagenicity testing and on definitive metabolic and pharmacokinetic studies to augment structure-activity predictions of carcinogenicity. (79 refs)

- 79-0019 Analyses of Epoxides, Haloethers and Related Compounds.** (Eng) Goldschmidt, B. M. (New York Univ. Medical Center, New York, NY, 70016). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977*. Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 113-119; 1978.

In attempt to distinguish between carcinogenic and noncarcinogenic exposures, female Swiss ICR/Ha mice were treated topically with 12 aliphatic monoepoxides starting at age 6 wk continuing for at least 1 yr. Of 30 animals treated with epoxypropanol, 8 developed papillomas that progressed to squamous carcinomas. Other active compounds were epoxybutene and epoxyhexadecane, which induced papillomas in 3/30 and 2/20 animals, respectively, but only one squamous carcinoma (epoxyhexadecane). In mouse skin tests with eight other monoepoxides (6 cyclic and 2 vicinal to a ring), only styrene oxide was active, inducing papillomas in 3/30 animals and one squamous carcinoma. Similar mouse skin studies with 11 aliphatic diepoxides revealed that, unlike the monoepoxides, most were carcinogenic. The incidence of papillomas, followed by the number of squamous carcinomas, caused by the most active compounds was as follows: 1,2,3,4-diepoxbutane, 10/30 (6); 1,2,4,5-diepoxypentane, 10/30 (3); 1,2,5,6-diepoxhexane, 13/30 (10); 1,2,6,7-diepoxheptane, 9/30 (1); 1,2,7,8-diepoxyoctane, 7/30 (4); and vinyl

cyclohexenediepoxyde, 14/40 (9). Studies of the reaction rates of the carcinogenic diepoxides with various nucleophiles showed that differences in second order rate constants were insufficient to distinguish between these compounds and the noncarcinogenic monoepoxides. Of 10 haloethers (α -chloroethers) tested by skin application or sc injection, 9 induced sarcomas by injection. The most potent compounds were bis(chloromethyl)ether (BCME) and chloromethyl methyl ether (CMME), which induced sarcomas in 21/50 and 10/30 animals, respectively. In the skin tests, BCME caused 13 papillomas and CMME no papillomas in 20 animals, which indicates that haloether carcinogenicity through skin application requires a bifunctional structure as in epoxides. The carcinogenic potential of a homologous series of haloethers related to BCME and CMME decreased with an increase in methylene groups between the two chloroether functions. (23 refs)

79-0020 The Carcinogenic Effect of Polycyclic Aromatic Hydrocarbons. (Ger) Contag, B. (Fachbereich Chemie, Technische Fachhochschule Berlin, Limburger Strasse 20, D-1000 Berlin 65, W. Germany). *Z Naturforsch C* 33(9/10): 651-659; 1978.

Theories on the mechanism of action of polycyclic aromatic hydrocarbons (electron, metabolite and matrix theories, the latter being a synthesis of some elements of the other two theories) are discussed. The matrix theory is based on the assumption that specific adsorption of the hydrocarbon molecules occurs on certain, as yet unknown, tissue components, and that there is a good geometric and energetic compatibility between these reaction partners. The function of the tissue component, e.g., an enzyme, can be inhibited by the adsorption of the carcinogen. Nuclear DNA is currently believed to be the receptor molecule for the carcinogen. This belief is supported by the fact that the covalent binding of the hydrocarbon molecules to the DNA bases implies a somatic mutation, and that the action of other carcinogens (aromatic amines, azo dyes, alkylants) can also be attributed to such a mechanism. The electrophilic metabolites of the polycyclic aromatic hydrocarbons also react, however, with a great number of other macromolecules, such as proteins. (79 refs)

79-0021 Quantum Chemically Based Predictions of Polycyclic Aromatic Hydrocarbon Carcinogenicity - The Bay Region Theory. (Eng) Lehr, R. E. (Univ. Oklahoma, Norman, OK, 73019); Levin, W.; Wood, A. W.; Conney, A. H.; Yagi, H.; Jerina, D. M. In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977*. Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 129-135; 1978.

In an attempt to determine the general importance of the diol epoxide pathway in the activation of polynuclear aromatic hydrocarbons to mutagens and carcinogens, quantum-chemical calculations were used to predict biological activity. A model was chosen that enabled calculation of the relative ease of benzylic carbonium ion formation from various diol epoxides based upon the finding that both cis- and trans- addition of water occurs in the hydration of the stereoisomeric benzo(a)pyrene 7,8-diol,10-epoxide. In order to assess the energy change that occurs upon the conversion of the diol epoxide to a benzylic triol carbonium ion, only the pi-electron energy change is considered. This calculation is then accomplished using the perturbational molecular orbital (PMO) approach. Results have shown a favorable correlation between predictions based upon the PMO calculations and the available data on mutagenicity and carcinogenicity of PAH and their derivatives: for a given PAH, diol epoxides in which the oxirane oxygen atom formed a part of a "bay region" were invariably calculated to be the most reactive metabolically possible diol epoxides of that PAH, and this evidence was confirmed by tests with benz(a)anthracene and its appropriate derivatives. (20 refs)

79-0022 Hydrazines: Occurrence, Analysis and Carcinogenic Activity as Related to Structure. (Eng) Schmeltz, I. (American Health Foundation, Valhalla, NY, 10595); Hoffmann, D.; Toth, B. In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977*. Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 172-178; 1978.

The occurrence, analysis and carcinogenic activity of hydrazines as related to structure are reviewed. Although hydrazines have received relatively little attention compared with other chemical carcinogens, a group of 37 hydrazines have been reported to induce tumors in laboratory animals. These include monoalkyl-, dialkyl- (symmetrical and unsymmetrical), trialkyl- and tetra-alkyl hydrazines, in addition to various hydrazides: maleic hydrazide, succinic acid-2,2-dimethylhydrazide, and isoniazid. Evidence suggests that most hydrazines are tumorigenic in the lungs and blood vessels, while all should be suspect pending animal studies. Degree of alkylation does not correlate with carcinogenic activity, and no structure-activity relations have been demonstrated except for a series of hydrazines where substitution on both nitrogens accounts for organospecificity. It is contended that different hydrazines have different mechanisms of action: hydrazine itself may react with a one- or two-carbon fragment during metabolism resulting in an acylating agent, or it may react directly with DNA to remove pyrimidine bases, although its exertion of tumorigenicity as an alkylating compound is difficult to visualize. Even though conclusive animal studies reveal the oncogenic nature of hydrazines as a group, epidemiological evidence is required before these observations are extrapolated to humans. (52 refs)

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- 79-0023 Metabolic Activation of Aromatic Amines.** (Eng) King, C. M. (Michigan Cancer Foundation, Detroit, MI, 48201). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977.* Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 140-147; 1978.

Enzymatic, cellular, and metabolic studies were reviewed in order to determine the complex molecular events involved in the metabolic activation of carcinogenic aromatic amines. One mechanism of activation of arylhydroxamic acids results from the formation of nitroxide-free radicals by one-electron oxidants. A second mechanism by which aromatic amine derivatives may be activated is based on the finding that seryl-transfer RNA synthetase could esterify 4-hydroxylaminoquinoline N-oxide to a product capable of reacting with nucleic acid. Additionally, an N-Oarylhydroxamic acid acyltransferase had been implicated in metabolic activation as follows: the acyl group is first transferred to the oxygen of the arylhydroxylamine, giving rise to an acyloxyamino derivative that can react spontaneously with nucleic acids or proteins. Even closely related tissues may differ widely in their susceptibility to tumor induction by a single compound as a result of different levels of an activating enzyme. The mutagenic potential of metabolic activation by acyltransferase was studied in *Salmonella typhimurium* strain TA 1538, which was exposed to the carcinogen acetylaminofluorene (AAF) in the presence and absence of an S-9 liver microsome fraction. The results showed that bacterial metabolism may be responsible for the terminal activation of 2-AAF derivatives. A good correlation was also demonstrated between the ability of arylhydroxamic acids to combine with nucleic acids and their ability to cause mutations in *Salmonella*. (18 refs)

- 79-0024 Polynuclear Aromatic Hydrocarbons: Occurrence, Formation, and Carcinogenicity.** (Eng) Hoffmann, D. (American Health Foundation, Valhalla, NY, 10595); Hecht, S. S.; Schmeltz, I.; Wynder, E. L. In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977.* Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 120-128; 1978.

A review of the occurrence, formation, and carcinogenicity of polynuclear aromatic hydrocarbons (PAH) is presented. PAH are formed during heating and combustion of fossil fuels and other organic compounds. Due to their characteristically low vapor pressures and water insolubility, they are ubiquitous in the environment, concentrating in particulate matter in the air, in water, in sediments, and in soil. The environmental synthesis of PAH is a two-step process: first, pyrolysis of organic matter leads to the formation of CH radi-

cals, and second, the radicals combine to produce thermodynamically preferred aromatic products. Epidemiological studies suggest that the main concern should be PAH content of tobacco smoke, air, and occupational settings, although it is known from model studies that PAH-containing inhalants do not necessarily induce lung cancer but rather act as initiators of malignancy for a subsequent insult by other carcinogens, cocarcinogens and promoters. Several four-ring parent and alkyl substituted aromatic hydrocarbons and many methylated and unsubstituted five- and six-ring hydrocarbons are carcinogenic in experimental animals. Most carcinogenic PAH have at least one free K-region and at least one unsubstituted angular ring. It is suggested that the carcinogenic PAH are metabolically activated in the angular ring to epoxides or dihydroxyepoxides. (52 refs)

- 79-0025 Aromatic Amines and Azo Dyes.** (Eng) Irving, C. C. (Veterans Administration Hosp., Memphis, TN). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977.* Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 136-139; 1978.

A review of the aromatic amines and azo dyes is presented. The most potent carcinogenic aromatic amines are those with two or three aromatic rings and with the amino group in the para position. A list of these active compounds includes benzidine, 2-naphthylamine, 4-aminobiphenyl, 2-aminofluorene, 4-aminostilbene, 2-aminophenanthrene, and 2-aminoanthracene. Monocyclic aromatic amines and aromatic amines with more than three rings are inactive or, at best, very weak carcinogens. Carcinogenic azo dyes are divided into two categories, the derivatives of p-aminoazobenzene, and those subject to reduction cleavage that yields carcinogenic aromatic amines. Structure activity relationships allow prediction of carcinogenic activity based on the reduction products of the azo compound. The reactions that are likely to be involved in the metabolic activation of aromatic amines are N-hydroxylation, conjugation, and acyl transfer, with one or more metabolic reactions (which are different in various susceptible tissues) requisite for oncogenicity. It is concluded that both the extent of metabolic activation and the absolute reactivity of the activated metabolites are highly dependent upon the structure of the aromatic amine. (17 refs)

- 79-0026 Hair Dyes and Breast Cancer (Letter to Editor).** (Eng) Burnett, C. M. (Clairol Inc., Stamford, CT, 06902); Menkart, J. *N Engl J Med* 299(22): 1253; 1978.

Factors that should be considered when evaluating the possible association between hair dyes and breast cancer are discussed. Almost all aromatic amines that induce breast cancer in rodents are conjugated or fused rings, whereas most oxida-

tive hair dyes are simple ring structures. In addition, none of 13 hair dyes tested in the NCI bioassay program caused cancer of the breast or any reproductive organ in mice. (11 refs)

- 79-0027 Complications of Prenatal Therapy with Diethylstilbestrol.** (Eng) Herbst, A. L. (Registry Res. Hormonal Transplacental Carcinogenesis, Chicago Lying-In Hosp., 5841 S. Maryland Ave., Chicago, IL, 60637); Scully, R. E.; Robboy, S. J.; Welch, W. R. *Pediatrics* 62(6, part 2, Suppl): 1151-1159; 1978.

Epidemiological, pathological, histological, and clinical data on clear cell adenocarcinoma (CCA) cases accessioned in the Registry for Research on Hormonal Transplacental Carcinogenesis (Chicago, Illinois) are reviewed, along with data on the histogenesis of diethylstilbestrol (DES)-associated genital abnormalities. The maternal hormone history was fully investigated in 292/333 registry CCA cases, and in approx 66% of the 262 cases the mother was treated with DES or the chemically related compounds dienestrol and hexestrol. Max daily doses of DES ranged from 1.5 to 150 mg, total doses from 135 to 18,200 mg. In most cases the drug was administered for high-risk pregnancy. The incidence curve shows a sharp rise beginning at age 14, a peak at age 19, and a sharp decline through age 22. Overall risk estimates of developing CCA range from 0.14 to 1.4/1,000 for DES-exposed women through age 24. CCA is diagnosed most efficiently by pelvic examination and cytology. Lower genital tract changes in DES-exposed women without cancer include vaginal adenosis, vaginal or cervical transverse ridges, and cervical ectropion. These changes are more common in women exposed in the second mo of fetal life or earlier. Vaginal changes in DES-exposed subjects may result from a disturbance of the müllerian epithelium and/or the vaginal plate, resulting in the persistence of müllerian cells at a level below that of their normal termination near the external os of the cervix. Similarly, the vaginal or cervical ridges may be the result of abnormal proliferation of connective tissue at the junction of the müllerian and urogenital-sinus anlage. Other observations suggest the possibility of a primary stromal action of DES. (28 refs)

- 79-0028 The Newborn Mouse as a Model for Study of the Effects of Hormonal Steroids in the Young.** (Eng) Kohrman, A. F. (Coll. Human Medicine, Michigan State Univ., East Lansing, MI, 48824). *Pediatrics* 62(6, part 2, Suppl): 1143-1150; 1978.

The use of fetal and neonatal mice to study the effects of steroidal and nonsteroidal compounds on development and carcinogenesis is discussed. Administration of estradiol, progesterone, testosterone, or diethylstilbestrol to mice younger than 5 days results in permanent vaginal and cervical changes in the adult with permanent alterations in the rates

of DNA, protein, and RNA synthesis in the affected tissues. A small but significant number of the animals treated with one of the first three hormones developed malignant lesions, mostly epithelial in nature, in the vaginal and cervical areas. The mouse appears to be an appropriate model for studying similar steroid-induced lesions in humans. Neonatal treatment with diethylstilbestrol appears to elevate cyclic AMP levels in the vaginal tissues. It is hypothesized that the primary effect of this treatment is to increase the rates of proliferation of the basal cell population from which the adult cervico-vaginal epithelium ultimately derives. The carcinogenesis resulting from neonatal or intrapartum steroid treatments may therefore be regarded as a form of teratogenesis. Cervico-vaginal changes have also been observed after neonatal treatment of mice with progestones. The mouse model may be useful for estimating the risk of further exposure to steroid hormones in women exposed to diethylstilbestrol in utero. It may also be useful in studies of prophylaxis of steroid-induced lesions or other abnormalities arising from neonatal challenges. (20 refs)

- 79-0029 Hormones and the Liver (Meeting Abstract).** (Eng) Lunzer, M. (Liver Unit, Dept. Gastroenterology, Royal North Shore Hosp., Sydney, NSW, Australia). *Aust NZ J Med* 8(6): 677; 1978. (no refs)

- 79-0030 General Discussion.** (Eng) Nordin, B. E. (MRC Mineral Metabolism Unit, General Infirmary, Great George St., Leeds LS1 3EX, England); Lemon, H. M.; Rakoff, A. E.; Utian, W. H.; van Keep, P. A.; Lauritzen, C.; Keller, P. J.; McKay Hart, D.; Van der Does, C.; Studd, J. W.; Kopera, H.; Rauramo, L.; Baulieu, E. E.; Neves e Castro, M.; Mack, T. M.; Haspels, A. A.; Vooijs, G. P.; Thijssen, J. H.; de Waard, F. In: *Front Horm Res* 5: 248-260; 1978.

A general discussion of papers presented at a conference on the risks and benefits of estrogen therapy is reported. It was concluded that the epidemiologists have made a very strong case for there being some connection between estrogen therapy and an increased risk of endometrial cancer, but as far as breast cancer is concerned the question is still open. However, estrogen therapy is still valuable for the treatment and prevention of estrogen deficiency. (no refs)

- 79-0031 Clinical and Experimental Aspects of the Anti-Mammary Carcinogenic Activity of Estriol.** (Eng) Lemon, H. M. (Dept. Internal Medicine, Univ. Nebraska Medical Center, 42nd St. and Dewey Ave., Omaha, NB, 68105). In: *Front Horm Res* 5: 155-173; 1978.

The results of a large-scale experiment in which estriol and 23 other natural and synthetic hormones were evaluated for antimammary carcinogenic activity in > 2,600 female Spra-

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gue-Dawley rats are reviewed, and brief mention is made of the effects of estriol on human postmenopausal metastatic breast carcinoma. Max reduction in the incidence of breast carcinomas (80%-90%) occurring during the natural life span of the rats was achieved when pellets containing 600-1,300 μg estriol were implanted sc every 2 mo, beginning 48 hr before po administration of 20 mg 7,12-dimethylbenz-(a)anthracene or 50-70 mg procarbazine (PC). Estriol doses that were lower or given more frequently than 100-200 $\mu\text{g}/\text{kg}/24$ hr every 2 mo were less effective. Estrone also significantly reduced breast carcinoma incidence; five other compounds produced a statistically insignificant reduction of incidence, especially in PC-treated rats. Estriol did not reduce the number of breast cancers induced by γ -radiation, and it did not reduce the incidence of other types of neoplasms. Estriol reduced the uterine wts of carcinogen-treated rats by 20%-25%. Estriol probably functions as a mammary anti-cocarcinogen by impeding ovarian estradiol stimulation of breast duct and alveolar cell replication, preventing the 10^{10} cell generations necessary for a palpable 1.0-cm tumor to become apparent. Experiments show that its action is comparable to that of castration. Human studies indicate excellent tolerance for po estriol doses of 10-200 $\mu\text{g}/\text{kg}/24$ hr, which may correct subnormal estriol/estrone + estradiol urinary quotients associated with elevated breast cancer risk. (36 refs)

- 79-0032 A Review of the Evidence Linking Estrogens and Cancer in Animals.** (Eng) Hertz, R. (Dept. Pharmacology, George Washington Univ. Medical Sch., Washington, DC, 20006). *Pediatrics* 62(6, part 2, Suppl): 1138-1142; 1978.

Evidence of the association between estrogen administration and subsequent tumor development in animals is reviewed. Tumors of the breast, cervix, endometrium, ovary, pituitary, testicle, kidney, and bone marrow have been induced reproducibly in the mouse, rat, rabbit, hamster, squirrel monkey, and dog by estrogens. However, the repeated failure of similar experiments to elicit a tumor response in rhesus monkeys has fostered skepticism of the potential relationship of these findings to humans. The animal studies have identified major critical factors in tumor induction by exogenous estrogens: genetic or ethnic derivation, dose, age, chronicity of exposure, and potential presence of predisposing viruslike factors. The genetic factor appears most applicable to humans, particularly in relation to breast cancer. Steroids exhibit a continuous spectrum of biological effects. The specificity of the biological effects of many steroids is relative rather than absolute, and a considerable degree of overlap is frequently encountered. There is a lack of specificity in the chemical structures of compounds having estrogenic and tumorigenic potency. The estrogenic response among hormonally induced tissue effects has the least specific structural requirements. It is suggested that the estrogenic response alone can be elicited by a wide variety of chemical agents. (37 refs)

- 79-0033 Estrogen Receptor Binding and Growth of the Reproductive Tract.** (Eng) Clark, J. H. (Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77080); Hardin, J. W.; McCormack, S. A. *Pediatrics* 62(6, part 2, Suppl): 1121-1127; 1978.

The mechanism of action of estrogen and its relationship to normal and abnormal estrogen-induced growth are discussed. In hormone-sensitive cells, estrogen is bound to cytosol receptors (Rc) in the cell, the binding resulting in the formation of receptor-estrogen complexes that undergo translocation to acceptor or nonacceptor nuclear sites. Nuclear binding of these complexes results in the replenishment of Rc sites. A single injection of estradiol in a female rat stimulates all late uterotrophic events, whereas a single injection of estriol or dimethylstilbestrol stimulates all early uterotrophic events but not uterine growth. Serial injection of estriol or use of estriol implants results in true uterine growth. Nonsteroidal estrogen antagonists are slowly cleared from their nuclear binding sites and cause prolonged stimulation of uterine growth. These compounds appear to have estrogenic properties in some cell types (epithelium), while acting as estrogen antagonists in others. Differential stimulation of the epithelial cells may account for the tumorigenic effects of nafoxidine and clomiphene. It is suggested that estrogen agonists and antagonists should be classified as short-acting or long-acting, the long-acting estrogens being further subdivided into two classes. Great caution should be applied when long-acting estrogens are used in humans. (32 refs)

- 79-0034 Neuroleptic-induced Prolactin Level Elevation and Breast Cancer. An Emerging Clinical Issue.** (Eng) Schyve, P. M. (Lab. Biological Psychiatry, Illinois State Psychiatric Inst., 1601 W. Taylor St., Chicago, IL, 60612); Smithline, F.; Meltzer, H. Y. *Arch Gen Psychiatry* 35(11): 1291-1301; 1978.

Literature on the possible link between breast cancer (BC) and prolactin (PL) is reviewed, particularly the evidence that neuroleptics may increase BC risk via their effects on PL secretion. All available neuroleptics, including reserpine, raise serum PL levels by limiting the interaction of dopamine with receptors that, by an unknown mechanism, markedly suppress PL secretion. In addition, there is a strong interaction between estrogens and reserpine or phenothiazines in disinhibiting PL secretion. Reserpine was significantly more effective in increasing plasma PL levels in rats given exogenous estrogen than in control rats. An elevated serum PL level increases the incidence of spontaneously occurring mammary tumors in mice and increases the growth of established carcinogen-induced mammary tumors in rats. However, caution is necessary in extrapolating experimental data to human mammary tumors, because human and rodent tumors differ in some important characteristics, including hormone responsiveness. Serum PL levels in women with, or at risk for, BC have generally been normal, and only a minority of human mammary tumors have been found to respond to

changes in serum PL levels. Epidemiologic studies have failed to demonstrate an increased risk of BC associated with the use of neuroleptics or reserpine. Thus, although some human mammary tumors are PL-dependent, the available evidence does not demonstrate an increased risk of BC in women receiving neuroleptics. (136 refs)

79-0035 Relationships Between the Epidemiology and Endocrinology of Mammary Carcinoma. (Eng)

de Waard, F. (Instituut voor Sociale Geneeskunde, Rijksuniversiteit Utrecht, Bijlhouwerstraat 6, Utrecht, Netherlands). In: *Front Horm Res* 58: 145-154; 1978.

Current information on the epidemiology of breast cancer is reviewed and related to endocrinological factors. The roles of prolactin, androgens, and estrogens are summarized briefly. The relationship between breast cancer and menopause, geographical differences in the incidence of breast cancer, and the relationship of body size and the development of breast cancer are also discussed. Age-specific incidence curves suggest that from an epidemiologic point of view, breast cancer occurring before and after menopause are two different entities. Differences in incidence between Western and non-Western countries are more profound after menopause than before. It is not desirable to adjust wt for height when analyzing the effects of wt and height on breast cancer risk; actually, height itself has been shown to be a risk factor. Further experiments should be aimed at investigating the relation of androgen and estrogen metabolism to body size and mass. (38 refs)

79-0036 Postmenopausal Carcinoma as a Result of Estrogen Treatment: Survey of Evidence. (Eng)

Mack, T. M. (Dept. Community and Family Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90007). *Pediatrics* 62(6, part 2, Suppl): 1104-1113; 1978.

Recent studies of the relationship between exogenous estrogen administration and endometrial cancer are reviewed, along with objections to these studies. The objections are classified into three groups: illogical, logical but cannot reasonably explain the available data, and logical and applicable. Findings that positively support an etiologic hypothesis are the magnitude of the relative risk estimates, the consistency of the studies internally and externally, the consistency of the internal evidences of interaction (dose-response or duration-response relationships, tendency for highest risk from estrogen to occur in women normally at low risk) with a biologic relationship, and the specificity of the association with respect to other drugs, which rules out a nonspecific ascertainment bias. Credibility is enhanced by a lack of specificity in the findings with respect to various classes of steroidal and nonsteroidal estrogens. Two important criticisms remain to be answered. The first is the possibility that estrogen use is only a surrogate for another determinant of endometrial cancer. A woman may be at high risk either

because of her treatment or because of the reasons she was selected for treatment. The second is the possibility that some or all of the association is due to pathologists conservatively or mistakenly classifying hyperplasia as neoplasia. However, the bulk of evidence from reevaluation studies is strongly against an explanation based on misclassification of hyperplasia. Even when the most serious reservations are considered, it is difficult to avoid the tentative conclusion that estrogens are causally linked to endometrial cancer and that the attributable risk is numerically sizeable. (34 refs)

79-0037 Uterine Cancer and Estrogen Therapy. (Eng)

Mack, T. M. (Cancer Surveillance Program, Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90007). In: *Front Horm Res* 5: 101-116; 1978.

Recent studies of the relationship between exogenous estrogen administration and endometrial cancer are reviewed, along with objections to these studies. The objections are classified into three groups: illogical, logical but cannot reasonably explain the available data, and logical and applicable. Findings that positively support an etiologic hypothesis are the magnitude of the relative risk estimates, the consistency of the studies internally and externally, the consistency of the internal evidences of interaction (dose-response or duration-response relationships, tendency for highest risk from estrogen to occur in women normally at low risk) with a biologic relationship, and the specificity of the association with respect to other drugs, which rules out a nonspecific ascertainment bias. Credibility is enhanced by a lack of specificity in the findings with respect to various classes of steroidal and nonsteroidal estrogens. Two important criticisms remain to be answered. The first is the possibility that estrogen use is only a surrogate for another determinant of endometrial cancer. A woman may be at high risk either because of her treatment or because of the reasons she was selected for treatment. The second is the possibility that some or all of the association is due to pathologists conservatively or mistakenly classifying hyperplasia as neoplasia. However, the bulk of evidence from reevaluation studies is strongly against an explanation based on misclassification of hyperplasia. Even when the most serious reservations are considered, it is difficult to avoid the tentative conclusion that estrogens are causally linked to endometrial cancer and that the attributable risk is numerically sizeable. (33 refs)

79-0038 Oral Contraceptives--Possible Mediation of Side Effects via an Estrogen Receptor in Liver.

(Eng) Eisenfeld, A. J. (Yale Univ. Sch. Medicine, New Haven, CT, 06510); Aten, R. F.; Weinberger, M. J. *Biochem Pharmacol* 27(22): 2571-2575; 1978.

A review of evidence is presented to support the concept that most of the side effects caused by oral contraceptives (throm-

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bosis, heart attacks, hypertension, gallbladder disease and liver tumors) are due to an estrogen interaction in the liver. Estrogen binding was readily detectable in liver cytosol prepared from adult female rats. The liver estrogen receptor increases 5- to 10-fold at about the time of puberty in the rat. The cytoplasmic receptor-steroid complex translocates from the cytoplasm to the nucleus, where it attaches to chromatin. The translocation has been demonstrated both in vitro and in vivo in rats. If some of the major side effects of oral contraceptives are mediated by a receptor-estrogen interaction in liver, their safety might be improved if this liver interaction could be minimized while maintaining the useful effects in the hypothalamic-pituitary axis and in the endometrium. This goal might be accomplished by exploiting some functional difference between the estrogen receptor in the hypothalamus, pituitary, and uterus. The newer combined oral contraceptives contain lower amounts of both the estrogen (ethinyl estradiol) and of the progestin. Decreasing the amount of ethinyl estradiol to 30 µg appears to retain contraceptive effectiveness, but it is not yet known whether this decrease will reduce the risk of thrombosis or of the other side effects. (43 refs)

- 79-0039 **Endometrial Response to Different Estrogens.** (Eng) Myhre, E. (Inst. Pathology, Rikshospitalet, Univ. Oslo, Oslo 1, Norway). In: *Front Horm Res* 5: 126-144; 1978.

Information concerning endometrial response to estrogen therapy, particularly in perimenopausal and postmenopausal women, is reviewed, and the author's experiences with endometrial bleeding and cystic glandular hyperplasia are contributed. There are two general criticisms of several previous studies: the dosage, mode of administration, and particularly the estrogenic preparation itself have not received sufficient attention. Furthermore, endometrial cancer has often been identified after relatively short courses of estrogen therapy (eg, 6 mo), while the latent period has often been of very short duration. This evidence appears to run contrary to the generally observed course of cancer induction, in which latent periods are often decades in length. It is suggested that what has actually occurred in these cases is an identification of existing neoplasms. Estrogen therapy has often been implicated as a source of post-menopausal bleeding. Of 259 patients followed 1-3.5 yr after treatment with estriol (213 patients; 2-4 mg/day) or estradiol (46 patients; same dose) by a regimen of 3 wk on treatment and 3 days off treatment, only 7 patients experienced slight bleeding (3 from the estriol group). No bleeding occurred when estriol treatment was ≤2 mg, or estradiol treatment was 1 mg. Cystic glandular hyperplasia, generally considered to be caused by estrogens from various sources, was studied in 204 patients over the age of 45 yr. There was a very high incidence of cases in the group age 48-56 yr. The gynecologists of these patients were interrogated by questionnaire, which revealed that only 14 patients (6.9%) had received previous estrogen therapy. It is advised, however, that women with already high blood-estrogen levels

should not be treated with endometrium-proliferating estrogenic substances. (72 refs)

- 79-0040 **Estrogens and Endometrial Carcinoma. Opinion on Drug Commission Findings.** (Ger) Lauritzen, C. (Univ.-Frauenklinik, Prittwitzstrasse 43, 7900 Ulm, W. Germany). *Fortschr Med* 96(45): 2293-2294; 1978.

Estrogens are currently believed to be facultative cocarcinogens rather than direct carcinogens. They increase the risk of endometrial cancer under certain circumstances; ie, long-term, acyclic treatment with high doses without gestagens. (18 refs)

- 79-0041 **Do Oral Contraceptives Induce Myoma?** (Ger) Eder, M. (Pathologisches Institut der Universität, Thalkirchner Strasse 36, D-8000, Munich 2, W. Germany); Prechtel, K. *Munch Med Wochenschr* 120(5): 1662; 1978.

Estrogen treatment and the use of estrogen-containing oral contraceptives cause hypertrophy of the myometrium. It is impossible to establish a correlation between uterine myoma and the use of estrogen preparations on the basis of autopsy series. (no refs)

- 79-0042 **Estrogen Therapy in the Young. Treatment of Turner's Syndrome with Estrogen.** (Eng) Levine, L. S. (Dept. Pediatrics, Div. Pediatric Oncology, Cornell Univ. Medical Coll., New York, NY, 10021). *Pediatrics* 62(6, part 2, Suppl): 1178-1183; 1978.

The use of estrogens in the treatment of Turner's syndrome is reviewed. Estrogen therapy in gonadal dysgenesis (GD) patients is likely to provoke endometrial hyperplasia, with the possible risk of subsequent development of endometrial carcinoma (EC). Data on the 10 literature cases of EC following estrogen therapy of GD patients are tabulated. In Turner's syndrome, there may be an increased susceptibility or genetic predisposition to EC development with estrogen treatment. (35 refs)

- 79-0043 **Effect of Prenatal Estrogen Exposure on Male Genitalia.** (Eng) Mills, J. L. (Dept. Pediatrics, Univ. Pennsylvania Sch. Medicine, Philadelphia, PA, 19104); Bongiovanni, A. M. *Pediatrics* 62(6, part 2, Suppl): 1160-1165; 1978.

Evidence of a relationship between maternal exposure to estrogen [particularly diethylstilbestrol (DES)] during pregnancy and later abnormal development of the urogenital sys-

tem of male offspring is reviewed. In one representative animal study, 15/24 male offspring suffered a variety of testicular changes: retention of one testis in the abdomen; epididymal cysts; hypoplastic, atrophic, and often calcified testes; inflammation of the seminal vesicles; nodules of the coagulating glands; and sterility. Repeated human studies have failed to uncover any relationship between prenatal estrogen exposure and male carcinoma, but a massive study of 50,282 pregnancies determined that there was an increased relative risk of birth defect development after DES exposure (1.56) and after ethinyl estradiol exposure (1.89). Specific malformations related to these exposures included hypospadias, eye and ear malformations, and Down's syndrome, but the numbers were too small to be statistically significant. Four case reports of congenital ambiguity following estrogen exposure in utero are summarized, in which the external genitalia ranged from normal female to male with hypogonadism. Abnormal testes were a common feature. In a case-control study of 163 men exposed to DES during fetal life, significant numbers of epididymal cysts, hypotrophic testes, hypoplastic penis and severely pathologic semen (Eliasson scale) occurred in the cases. Furthermore, significantly fewer cases had ejaculate volumes of 1.5 ml or more. There was no correlation between abnormal semen quality or genital anomalies and dose or time of commencement of DES therapy. The question still remains as to whether these exposed men will develop new or different types of abnormalities as they age. (36 refs)

- 79-0044 Experimental Colon Cancer.** (Eng) LaMont, J. T. (Div. Gastroenterology, Peter Bent Brigham Hosp., 721 Huntington Ave., Boston, MA, 02115); O'Gorman, T. A. *Gastroenterology* 75(6): 1157-1169; 1978.

Information regarding the chemistry, metabolism, and mechanism of action of the more widely used colon carcinogens and the biology of the tumors they produce is reviewed. Several potent and specific chemical carcinogens produce in laboratory rodents a very accurate animal model of human colon cancer. Colon cancers have been produced with cholanthrenes, aromatic amines, hydrazine derivatives, alkylnitrosamides, and aflatoxin. The most potent and specific agent is 1,2-dimethylhydrazine (DMH). DMH undergoes metabolic activation in the host to the active carcinogen methyl-diazonium, an alkylating agent. This activation does not require intestinal flora, because DMH-treated germ-free animals also develop colonic tumors. The activated carcinogen reaches the colon by the blood stream or the fecal stream, and its primary effect in the colonic epithelial cell is methylation of DNA. The effect is not specific for the colon, because it also occurs in the liver and kidney, which are not target organs for DMH. After several days of reduced DNA synthesis, there is an increase in cellular proliferation and a widening of the proliferative zone. After 2-3 mo of treatment, there is a decrease in goblet cells, hyperplasia of the glands, and areas of focal atypia. Microscopic adenocarcinomas and adenomatous polyps appear after 4-6 mo, and they eventually produce rectal bleeding or bowel obstruction. Tumor yield

is affected by alteration in dietary fat, administration of bile salts and cholestyramine, and nonspecific colonic injury. The mechanism of these interactions is not known. The antigenic properties of colon cancers and the host-immune defenses directed against these tumors are strikingly similar in animals and humans. Although caution must be exercised in extrapolating the results of animal studies to human disease, animal models will hopefully expand the knowledge of a fundamental biology of colonic neoplasia. (160 refs)

- 79-0045 Carcinogenic Natural Products.** (Eng) Weisburger, E. K. (NCI, Bethesda, MD). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977*. Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 184-192; 1978.

A review is presented of carcinogenic compounds occurring naturally in plants and fungi. Studies have shown tobacco to contain nitrosamines, hydrazine, vinyl chloride, benz(a)pyrene, and polycyclic aromatic hydrocarbons, all proven carcinogens. The nut of the cycad plant, sometimes used as a source of starch, may contain cycasin, which is known to induce carcinomas of the liver, kidney, and intestine in laboratory animals. The root of the Indian plant *Jammu calamus* was used as a flavoring for vermouth until it was discovered that β -asarone (85% of the flavoring material) caused intestinal tumors in rats, and a similar compound, estragole, from estragon and tarragon oil, was found to be hepatocarcinogenic in young male mice. Among fungal carcinogens, ethyl carbamate (urethane) has been shown to induce lung and liver tumors when administered to mice and newborn rats, respectively. Mycotoxins, particularly aflatoxin B₁ (and to a lesser extent B₂, G₁, and G₂) produced by the fungus *Aspergillus flavus* is an extremely potent carcinogen and readily contaminates many types of grains and oilseeds. Compounds produced by other fungi that have effects similar to aflatoxin B₁ include sterigmatocystin, elaiomyacin, griseofulvin, and streptozotocin. It is postulated that many other naturally occurring carcinogens are present in the environment, but these are generally thought to be weak or adequately defended against by normal detoxification mechanisms, repair enzymes, and natural protective substances in foods (eg, indole derivatives in vegetables). (49 refs)

- 79-0046 Laryngeal Cancer and Consumption of Alcohol and Tobacco (2 Letters to Editor).** (Eng) Brown, K. S. (Dept. Statistics, Univ. Waterloo, Waterloo, Ontario, Canada); Cherry, W. H.; Forbes, W. F.; McMichael, A. J. *Lancet* 2(8099): 1099; 1978.

A presumed error in reasoning in a study of the association between laryngeal cancer and alcohol and tobacco consump-

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tion among British and Australian men and women is pointed out to the author, and the author's reply is presented. It is suggested that the similar recent rises in esophageal cancer mortality in British men and women, occurring against a background of dissimilar smoking trends, may reflect an interactive effect between alcohol and tobacco. (1 ref)

- 79-0047 Actual Problems of Toxicology of Food Products.** (Rus) Nesterin, M. F. (Dept. Hygiene Nutrition, Inst. Nutrition, Moscow, USSR). *Zh Vses Khim O-Va DI Mendeleeieva* 23(4): 372-378; 1978.

A review is presented of current data on the incidence of various toxic substances in food products. In addition to pesticide residues, antibiotics, heavy metals, and hormones, various food products (especially smoked pork sausage) were found to contain hazardous levels of carcinogenic nitrosamines (up to 3.3 $\mu\text{g/kg}$). (58 refs)

- 79-0048 Carcinogenic N-Nitrosamines in Food Products.** (Rus) Kostiukskii, Ia. L. (Inst. Nutrition, Moscow, USSR); Arkhipov, G. N.; Malamed, D. B.; Zhukova, G. F. *Zh Vses Khim O-Va DI Mendeleeieva* 23(4): 406-410; 1978.

A review is presented summarizing current data on the incidence of various carcinogenic N-nitrosamines (NA) in food products. Depending on the method of analysis, the content of NA in meat samples ranged from 0.5 to 23.9 $\mu\text{g/kg}$. NA were detected in various fish products: the max content of NA was recorded in fish flour (2,000 $\mu\text{g/kg}$). (53 refs)

- 79-0049 Structure-Activity Studies on N-Nitroso Compounds and Their Precursors.** (Eng) Mirvish, S. S. (Eppley Inst. Res. Cancer, Omaha, NB, 68102). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977*. Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 158-162; 1978.

Current knowledge concerning the carcinogenicity of N-nitroso compounds is reviewed. Nitrosamines are formed from a reaction of nitrous acid with a secondary amine or a simple amide. Nitrous acid is formed from environmental nitrates via nitrites, and when amines are involved, the reactive species is N_2O_3 , formed from two molecules of nitrous acid. Therefore, the rate of nitrosamine production is proportional to the square of the nitrous acid concentration, and directly proportional to the amine concentration. Although there is a "stoichiometric" rate constant for this reaction, the "true" rate constant (k_2) is based only on non-ionized amine

and is therefore pH dependent. The relationship between $\log k_2$ and the pK_a of the amine is approx linear, and the optimum pH is known to be 3.4. The success of H_2NO_2 + attack on amides is dependent upon the charge of the amides' nitrogen atoms: the stronger the negative charge, the quicker the reaction. Tertiary amines can also yield nitrosamines and guanidines can form nitrosoarea, but the reactions are slow. Morpholine, piperazine, and methyl aniline fed to Swiss and Strain A mice for 20 wk while NaNO_2 was administered in drinking water induced adenomas in a manner consistent with the kinetics discussed above, while nitrite levels of 0.25 g/l produced no adenomas. Nitrosamine carcinogenicity as related to the air/water partition coefficient (K_1) and ether/water partition coefficient (K_2) of each compound was studied; as K_1 and K_2 increased within a class of nitrosamines, esophageal carcinogenicity increased while liver carcinogenicity decreased. (14 refs)

- 79-0050 Chemical Structure and Carcinogenesis of Nitrosamines.** (Eng) Lijinsky, W. (Frederick Cancer Res. Center, Frederick, MD, 21501). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977*. Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 148-157; 1978.

Studies of structure-activity relations in nitrosamines (NA's) are reviewed. Deuteration of dimethylnitrosamine or nitrosomorpholine and replacement of the α hydrogens of diethylnitrosamine or nitrosopyrrolidine by a methyl group results in appreciably lessened carcinogenic potency, consistent with the idea that rupture of an α -carbon-hydrogen bond is the limiting step in carcinogenesis by these compounds. Likewise, methylation of nitrosopiperidine (NP) at the 3- and 2-methyl positions results in progressively weakened carcinogenicity; the 2,6-dimethyl and 2,2,6,6-tetramethyl derivatives are noncarcinogenic. Of the dinitrosopiperazine derivatives, however, the parent compound, with no methyl groups, is the least potent and the 2,6-dimethyl derivative is the most potent, possibly due to the ability of the methyl groups to fix molecular conformation. The target organ of some NP's can be changed by replacing hydrogen in the 4-position with oxygen. The double bond also changes the organ specificity of certain compounds. Substituting chlorine atoms for hydrogen in NP greatly increases carcinogenicity. The findings raise the possibility that reactions related to hepatic carcinogenesis are not representative of the process in general. In any case, the α -hydrogens are not the rate-limiting step in all NA carcinogenesis. Studies in which the deuteration site was varied in a series of methylethylnitrosamines showed that oxidation at either carbon of the ethyl group and methylation were not related to carcinogenesis. The two 1-ethyl deuterated compounds produced liver tumors only, but the unsubstituted compound produced esophageal

phageal tumors as well. Thus, reactions leading to esophageal and liver carcinogenesis seem to be distinct. (28 refs)

- 79-0051 Nitrosamines in Animal Food (Letter to Editor).** (Eng) Lijinsky, W. (Frederick Cancer Res. Center, Frederick, MD, 21501). *Science* 202(4372): 1034; 1978.

A previously published briefing concerning the detection of nitrosamines in laboratory animal diets is discussed. The 50 ppb of nitrosodimethylamine (NDMA) found in the animal diets present no measurable risk to these animals, as they live only 2-3 yr; previous studies in rats fed higher concentrations of NDMA for a lifetime showed no carcinogenic effect, and there is little evidence of a synergistic effect of nitrosamines in carcinogenesis. While 50 ppb of NDMA might be significant if present in human food consumed for as long as 70 yr, its presence in the diets of experimental animals could have no bearing on the outcome of any experiment. (2 refs)

- 79-0052 On the Desirability of the Health Physics Society Assuming Responsibilities in Nonnuclear and Nonradiation Fields.** (Eng) Gammage, R. B. (Health and Safety Res. Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Thorngate, J. H.; Parkinson, W. W.; Hawthorne, A. R.; Vo-Dinh, T. *Health Phys* 35(5): 711-714; 1978.

The energy crisis places new demands on the Health Physics Society to expand its traditional and almost exclusive interest in ionizing radiation to embrace new energy system pollutants, particularly the chemical carcinogens. (12 refs)

- 79-0053 Common Sense and Environmental Pathology.** (Eng) Wagner, B. M. (No affiliation given). *Hum Pathol* 9(6): 733-734; 1978.

There is not yet unanimity within the scientific community regarding the extrapolation from laboratory animals to humans. The cause and effect relationship between cancer in humans and exposure to environmental chemicals is far too complex and too important to be determined on the basis of limited information. (3 refs)

- 79-0054 Lead Poisoning by Automobile Traffic.** (Ger) Blumer, W. (FMH Allgemeine Medizin, Ch-8754 Netstal, Switzerland). *Therapiewoche* 28(44): 8469-8470; 1978.

Evidence of a higher incidence of cancer in persons exposed to lead from automobile exhaust (AEX) (traffic police, inhabitants of high-traffic areas who also work on the street) is reviewed. This effect of AEX can be prevented by treat-

ment with Ca-EDTA; cancer mortality was 2% among 47 persons exposed to AEX who were treated with Ca-EDTA, compared with 13% among 185 exposed persons who were not treated. (15 refs)

- 79-0055 OSHA Issues New Arsenic Standard.** (Eng) Weinstein, G. L. (OSHA Office Carcinogen Standards). *Job Safety and Health Magazine* 6(7): 15-23; 1978.

Accumulated evidence has demonstrated that workers exposed to inorganic arsenic have been dying of lung cancer at 2-3 times the expected rate. The Occupational Safety and Health Administration has issued a final standard that establishes a permissible exposure limit of 10 $\mu\text{g}/\text{m}^3$ of air averaged over an 8-hr period. (no refs)

- 79-0056 Laws of Statistics Ignored by Statisticians (Letter to Editor).** (Eng) Cohen, B. L. (Dept. Physics, Univ. Pittsburg, Pittsburg, PA, 15260). *Health Phys* 35(4): 582-584; 1978.

A previous report on cancer mortality among workers at the Hanford plant ignored two basic laws of statistics: (1) given various statistical analyses for determining a result, one must not be influenced by the result in choosing which analysis to use; and (2) in the course of a series of statistical analyses, the stages at which results are reported must not be influenced by the results. In the Hanford report, a series of analyses were conducted, but only the one that gave a positive result was reported. (6 refs)

- 79-0057 Carcinogenic Possibilities in Foundry Operations.** (Eng) Scott, W. D. (Atlas Foundry and Machine Co., Tacoma, WA). *Foundry* 106(12): 48-55; 1978.

There is preliminary evidence that the incidence of lung cancer in a foundry is greater than that for the general public. The technology to measure potential carcinogens at trace levels is being developed. Among the proven carcinogens that will be found in some foundries are benzene, asbestos, arsenic, beryllium, and benzo(a)pyrene. (25 refs)

- 79-0058 DNA Repair and Its Coupling to DNA Replication in Eukaryotic Cells.** (Eng) Cleaver, J. E. (Lab. Radiobiology, Univ. California, San Francisco, CA, 94143). *Biochim Biophys Acta* 516(4): 489-516; 1978.

The three major systems for DNA repair (photoreactivation, excision repair, and postreplication repair) are reviewed. Photoreactivation appears to be vestigial. Mammalian cells have one major repair system, excision repair, with many branches (nucleotide excision repair, base excision repair,

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crosslink repair, etc) and a multiplicity of enzymes. Any particular carcinogen produces a spectrum of damaged sites, and each kind of damage may be repaired by one or more branches of excision repair. In various genetic or physiologically normal or abnormal states, these different branches may have different relative importance. Excision repair is rarely complete, except at very low doses, and eukaryotic cells survive and replicate DNA despite the presence of unrepaired damage. When investigating repair and replication in various diseases, it is important to realize that these systems interact. Many alterations in replication in damaged cells may be secondary consequences of excision repair. Similarly, increases in sensitivity to radiation or carcinogens in many diseases may represent secondary consequences of other defects that alter DNA replication and its coupling with repair. (184 refs)

- 79-0059** Influence of Environmental Factors Excluding Ultra Violet Radiation on the Incidence of Skin Cancer. (Eng) Everall, J. D. (Skin Dept., Royal Marsden Hosp., London SW3, England); Dowd, P. M. *Bull Cancer (Paris)* 65(3): 271-279; 1978.

The recognized environmental causes (except UV radiation) of skin cancer (SC) are reviewed. Although SC is the most common form of cancer in the United States, accurate incidence rates are rarely available, because SC is very often curable and only infrequently results in death. Three principal groups of physical and chemical agents are known to cause SC: polycyclic aromatic hydrocarbons (PAH) inorganic arsenic, and radiation. PAH carcinogenesis occurs in areas of skin that are in contact with these carcinogens, usually of the benzopyrene and benzantracene families, which are products of the combustion and distillation of carbonaceous materials. The scrotum seems particularly susceptible. Previous studies have shown an increased risk of scrotal cancer in cotton mule spinners (62/1,000 men versus 1.8/1,000 men in other occupations) and in wax pressmen, employed ≥ 10 yr (806/100,000 population versus 0.15/100,000 in the general population). Pitchworkers had an 11-fold increased incidence of cutaneous squamous cell carcinoma. Whereas mortality in England and Wales from scrotal cancer is declining overall, the incidence of scrotal epithelioma continues to rise in the Birmingham area, being four times the expected value. Inorganic arsenic can be carcinogenic at any site following its inhalation and ingestion. Although documented cases are scarce, outbreaks of arsenical cancer following water supply contamination or pesticide use have occurred, resulting in an excess incidence of skin cancer. Ionizing radiation produces chiefly basal cell and squamous cell carcinomas at the sites of exposure. The average dose required to induce cancer appears to be approx 3,000 rems, and many fractionated doses over a long period are more harmful than a few large doses over a short time. (5 refs)

- 79-0060** Infrared Radiation as a Carcinogenic Agent (Letter to Editor). (Eng) Schwartz, R. A. (Ros-

well Park Memorial Inst., Buffalo, NY, 14263). *Br J Dermatol* 99(4): 460-461; 1978.

The role of infrared (IR) radiation in electromagnetic wave-induced carcinogenesis is discussed. Since most studies concerning radiation-induced skin cancer have involved the UV spectrum, there is a deficit of work involving the spectrum of 700-1,000,000 nanometers. At least one study has suggested that IR radiation is implicated in erythema ab igne and that IR may penetrate the epidermis and dermis. Since erythema ab igne predisposes to skin cancer, further studies of the relationship between IR irradiation and carcinogenesis are warranted. (11 refs)

- 79-0061** Increased Sensitivity of Xeroderma Pigmentosum Skin Fibroblasts to Carcinogenic Compounds (Letter to Editor). (Eng) McCormick, J. J. (E. Lansing, MI); Maher, V. M. *Arch Dermatol* 114(11): 1716; 1978.

Xeroderma pigmentosum (XP) cells are more sensitive than normal cells to the induction of mutations by low doses of UV light and polycyclic aromatic hydrocarbons, a finding that may be causally related to the enhanced cancer-prone condition of XP patients. XP cells are also more sensitive to several other classes of carcinogens, including aromatic amides, 4-nitroquinoline 1-oxide, and aflatoxins. (3 refs)

- 79-0062** Xeroderma Pigmentosum; Heterogeneous Syndrome and Model for UV Carcinogenesis. (Eng) Jung, E. G. (Hautklinik der Stadtischen Krankenanstalten, Postfach 23, D-6800 Mannheim, W. Germany). *Bull Cancer (Paris)* 65(3): 315-321; 1978.

A review is presented of xeroderma pigmentosum, a rare autosomal recessive genetic disease characterized by sun sensitivity, pigment anomalies, and multiple cutaneous neoplasms. It is hypothesized that patients are susceptible to these neoplasms at least partly because of disease-caused abnormalities in the self-protecting mechanisms of excision repair, photoreactivation, postreplication repair, and gap filling repair, which are usually active after UV irradiation-induced DNA mutation. Gene frequency is about $2.5/10^6$ in the overall population, and the frequency of XP heterozygotes is 0.2% to 0.5%. Different genetic variants of XP, although phenotypically similar, are separate entities causing different effects on the repair systems. These phenotypic manifestations, which include blistering after sun exposure, melanotic precanceroses, multiple melanoma, actinic keratoses, and multiple skin malignancies in sun exposed areas, are graded in severity and maintain intrafamilial constancy. When the gradations in severity are considered with determination of the rate of DNA repair and with cell fusion studies, XP can be differentiated into six known complementation groups, including the De Sanctis-Cacchione syndrome and the XP-variant type. There is evidence that the number of sister

chromatid exchanges per metaphase in XP is increased after UV irradiation in vitro, which is good evidence that XP cells are prone to UV-induced mutations that possibly lead to the initiation of cancer. (25 refs)

79-0063 Human Disorders Showing Increased Sensitivity to the Induction of Genetic Damage. (Eng)

Arlett, C. F. (MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton BN1 9QG, England). *Annu Rev Genet* 12(1): 95-115; 1978.

Disorders involving increased sensitivity to the induction of genetic damage or defects in the ability of cells to repair DNA damage are reviewed. Clinical descriptions of xeroderma pigmentosum (XP), ataxia telangiectasia (AT), Fanconi's anemia, Bloom's syndrome, and Cockayne's syndrome are presented, and cellular anomalies associated with these conditions are described. In addition, mutagen sensitivity among patients with these disorders, DNA repair, and mutagen sensitivity in other disorders (eg, Down's syndrome, progeria) are reviewed. In XP, defects in DNA repair result in elevated levels of UV-induced mutations. UV-induced mutations probably arise during replication of unexcised damage, so that the hypermutability of XP strains results either from more lesions being replicated (excision-defective XP) or from increased susceptibility to errors of the defective postreplication repair (XP variants). In the somatic mutation theory of carcinogenesis, this hypermutability will lead to an increase in the level of UV-induced skin cancers, a principal symptom of the disorder. Although the neurological abnormalities found in some XP patients clearly cannot be a consequence of UV irradiation, a correlation has been discovered between the sensitivity of different XP cells to UV and the occurrence of neurological abnormalities in the donors. Defects in DNA repair after treatment of AT cells with γ -rays and Fanconi cells with mitomycin C are not associated with hypermutability by these agents. There is therefore no ready explanation for the elevated incidence of cancer in these disorders in terms of increased mutation rates. The lymphoreticular tumors in AT patients are probably associated with defects in the immune system. Although molecular explanations for the cellular observations in AT and Fanconi's anemia are rapidly evolving, there is presently no obvious relationship between the different defects in DNA repair and most of the clinical symptoms. Although Bloom's syndrome has many features in common with those of Fanconi's anemia and AT, no defect in DNA repair has yet been discovered. Molecular and cellular studies have certain direct clinical applications, especially in that they provide the possibility of early and reliable diagnosis. (125 refs)

79-0064 Hazards of "Low Dose" Irradiation to the Head and Neck. (Eng) Kaplan, E. L. (Chicago, IL). *Curr Surg* 35(6): 371-372; 1978.

Information concerning the long-term effects of low-dose irradiation to the head and neck is summarized briefly. Significant numbers of benign and malignant thyroid and salivary gland tumors are being discovered in patients 20-30 yr after they had received doses of $\leq 1,500$ rads (even a dose as low as 6.5 rads) to the head and neck region. (no refs)

79-0065 Twenty Years of Virusogenetic Theory of Tumor Development. (Rus) Ageenko, A. I. (P. A. Hertsen Res. Oncological Inst., Moscow, USSR). *Vopr Onkol* 24(11): 106-116; 1978.

This review summarizes the results and discusses the outlooks of the viral theory of tumorigenesis. The central dogma of the oncogenic virus hypothesis (that the integration of a viral genome is essential for stable transformation) had been proven in numerous direct experiments with small DNA-containing oncornaviruses and on some of the herpesviruses. The hypothesis is a cornerstone of more general theories and concepts (virogene or provirus hypotheses). Application of the oncogenic virus theory to the mechanisms of neoplastic transformation revealed that the virions of the oncornaviruses contain the enzyme reverse transcriptase, proved the widespread occurrence of some oncornaviruses (C type) among vertebrates revealed the vertical transmission of oncornaviruses, showed the possibility of induction of endogenous viruses by various carcinogens and mutagens, and determined the gene sequence in virion RNA in certain avian and rodent oncornaviruses. (46 refs)

79-0066 DNA Polymerases of Normal and Neoplastic Mammalian Cells. (Eng) Sarngadharan, M. G. (Litton Bionetics, Inc., 7300 Pearl St., Bethesda, MD, 20014); Robert-Guroff, M.; Gallo, R. C. *Biochim Biophys Acta* 516(4): 419-487; 1978.

The properties and possible functions of the DNA polymerases identified in normal, malignant, and virus-infected cells are reviewed. Mammalian cells contain at least three distinct DNA polymerases: DNA polymerase α appears to be responsible for chromosomal DNA replication, and DNA polymerase β seems to be involved in DNA repair; the role of DNA polymerase γ is not well understood. A fourth DNA polymerase, mitochondrial DNA polymerase, may prove to be the same as DNA polymerase γ . Infection by certain viruses causes cells to express additional DNA polymerases that are remarkably specific and are extremely useful as markers to detect viral infection in cells. Fidelity, the most crucial aspect of DNA replication in vivo, is controlled in prokaryotic systems by choice of the complementary nucleotide and by a "proofreading" activity associated with the DNA polymerase. The proofreading activity is not possessed by mammalian cellular DNA polymerases. Certain DNA polymerases show a high error rate in DNA synthesis in vitro, and fidelity levels can be further reduced by certain mutagenic/carcino-

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genic metal ions. The terminal deoxyribonucleotidyltransferase may also contribute to somatic mutation in eukaryotes. The use of long-established tissue culture cell lines to study cellular DNA polymerase may present problems associated with contamination, so it is preferable to use fresh tissues or short-term-cultured cells. The use of cells infected by small DNA viruses (ie, polyoma virus or simian virus 40) will be extremely useful for the study of DNA replication in mammalian cells. (512 refs)

- 79-0067 RNA Tumor Viruses.** (Ger) Bauer, G. (McArdle Lab. Cancer Res., Univ. Wisconsin, 450 N. Randall Ave., Madison, WI, 53706). *Naturwiss Rundsch* 31(11): 445-455; 1978.

The structure of RNA tumor viruses, viral genes, gene products, defective and nondefective sarcoma viruses, reverse transcriptase, provirus synthesis, and the replication cycle of RNA tumor viruses are described. The mechanism of virus-induced transformation is still unclear. (20 refs)

- 79-0068 In Vitro Determination of Potential Benefits and Risks of Photodynamic Therapy (Meeting Abstract).** (Eng) Marrichi, J. E. (Bureau Radiological Health, Food and Drug Admin., Dept. Health, Education and Welfare, Rockville, MD, 20857); Brewer, P. P.; Goddard, J. G. *Health Phys* 35(6): 891-892; 1978. (1 ref)

- 79-0069 Epstein-Barr Virus DNA in Tumour Tissue from Native Alaskan Patients with Nasopharyngeal Carcinoma (Letter to Editor).** (Eng) Lanier, A. (Center Disease Control, Anchorage, AK, 99501); Bender, T.; Talbot, M.; Clift, S.; Tschopp, C.; Dohan, P.; Bornkamm, G.; Henle, W. *Lancet* 2(8099): 1095; 1978.

Studies demonstrating the presence of Epstein-Barr virus DNA in the tumor tissue of four Eskimo or Aleut patients with nasopharyngeal carcinoma are discussed. These findings add further strength to the association of nasopharyngeal carcinoma with Epstein-Barr virus. (6 refs)

- 79-0070 Role of Antibodies in Neoplasia.** (Pol) Strzelecka, G. (Zaklad Mikrobiologii i Immunologii, Instytut Patologii i Farmakologii PAM, al Powstancow Wlkp. 72, 70-111 Szczecin, Poland); Halasa, J.; Dabrowski, W. *Pol Tyg Lek* 33(46): 1801-1804; 1978.

Studies of the role of antibodies and antigens in tumor growth and their implications for cancer immunotherapy are reviewed. (35 refs)

- 79-0071 Interactions in the Natural History of Aging and Carcinogenesis.** (Eng) Pitot, H. C. (Dept. Oncology, McArdle Lab. Cancer Res., Medical Sch., Univ. Wisconsin, Madison, WI, 53706). *Fed Proc* 37(14): 2841-2847; 1978.

Proposed relationships between the various aspects of carcinogenesis and the aging process are discussed. The three stages of carcinogenesis are tumor initiation, promotion, and progression. In cultured mammalian fibroblasts (especially human), the first stage of aging involves initiation of the primary culture; the second stage is a period of vigorous replication; and the third stage is a period of declining mitotic potential culminating in cell death. During the last phase, aging cells lose their ability to replicate, becoming arrested in G₁. Cells in this stage may not be easily transformed, since continuous cell division and DNA synthesis are essential for expression of the transformed state. This implication that tumor promotion becomes less efficient as the aging process continues suggests that the later stages of carcinogenesis are modified by intrinsic cellular changes as well as by hormonal, immunologic, and nutritional factors. (66 refs)

- 79-0072 Genes on Chromosome 7 (Meeting Abstract).** (Eng) de la Chapelle, A. (Dept. Medical Genetics, Univ. Helsinki, Helsinki, Finland). *Clin Genet* 14(5): 285; 1978. (6 refs)

- 79-0073 Defective DNA Repair and Hereditary Diseases (Meeting Abstract).** (Eng) Cleaver, J. E. (Lab. Radiobiology, Univ. California, San Francisco, CA, 94143). *Can J Genet Cytol* 20(3): 431-432; 1978. (no refs)

- 79-0074 Chromosome Studies in Polycythemia Vera.** (Eng) Wurster-Hill, D. H. (Dept. Pathology, Dartmouth Medical Sch., Hanover, NH, 03755); McIntyre, O. R. *Virchows Arch Cell Pathol* 29(1/2): 39-44; 1978.

Polycythemia vera (PV) represents an apparent monoclonal stem cell proliferation with a frequent transition to full neoplastic transformation. Of untreated PV patients, up to 26% have some chromosome abnormalities in the marrow at the time of diagnosis, and 10%-15% have an abnormal cell line or clone. Both structural and numerical aberrations occur. Aneuploidy is the most common chromosome abnormality, however, with hyperdiploid clones occurring more frequently than hypodiploid clones. Chromosomes 1, 8, 9, and 20 are involved in a nonrandom pattern, and aberrations of the F group, at least of chromosome 20, are associated to some extent with diseases involving erythroid hyperplasia. Leukemia develops in a certain percentage of patients, regardless of the type of treatment they have received, but the relationship between the chromosome abnormalities and the develop-

ment of leukemia is still unclear. The abnormal clones that occur in PV are quite stable, and there is no indication that they correlate with a prognosis of leukemic transformation. (no refs)

79-0075 Chromosome Mutation: Various Times, Various Cells (Meeting Abstract). (Eng) German, J. (Lab. Human Genetics, New York Blood Center, New York, NY, 10021). *Can J Genet Cytol* 20(3): 432-433; 1978. (no refs)

79-0076 Human Genetics Disorders Causally Relating DNA Repair Deficiency and High Risk of Cancer (Meeting Abstract). (Eng) Paterson, M. C. (Biology and Health Physics Div., Atomic Energy of Canada Ltd., Chalk River, Ontario KOJ 1J0, Canada). *Can J Genet Cytol* 20(3): 452; 1978. (no refs)

79-0077 Tumors as Clonal Proliferation. (Eng) Nowell, P. C. (Dept. Pathology, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104). *Virchows Arch Cell Pathol* 29(1/2): 145-150; 1978.

A review is presented of the relationship of tumor biology to chromosome banding studies of human malignancies, and the clinically relevant implications involved. Cytogenetic studies disclose the fact that most tumors are clonal (unicellular in origin) and have karyotypic aberrations. These nonrandom alterations detected on chromosomes by banding studies seem to point out the sites where the genes important in neoplasia are situated. It is hypothesized that tumor development occurs as a result of genetic lability within the neoplastic clone that subsequently leads to the emergence of increasingly mutant subpopulations with more malignant traits. Within this theoretical framework, acute leukemia, chronic leukemia, and preleukemia can be viewed as differing only in the rate at which an aberrant clone is expanding, with progression to a more aggressive phase that reflects the emergence of a new predominant subpopulation as the result of an additional genetic change. (6 refs)

79-0078 Introduction to the Modern Classification of the Non-Hodgkin Malignant Lymphomas. (Fre) Heimann, R. (Service d'anatomie pathologique, Institut Jules Bordet, Centre des Tumeurs de l'Universite Libre de Bruxelles, Brussels, Belgium); Van den Heule, B. *Dermatologica* 157(6): 345-356; 1978.

Developments leading to the Lukes and Kiel classifications of non-Hodgkin's malignant lymphomas are reviewed. Both classifications are based on the discoveries of modern immunology and on the conclusion that lymphoma development occurs in two steps. There is first a block in lymphocyte

activation at a certain stage, after which the blocked clone becomes neoplastic and replaces the normal components of lymph nodes. The type of cells observed in various lymphomas therefore depends on the stage of arrest in lymphocyte transformation. Although the two classifications rely on marker techniques for the identification of T, B, and U (undefined) lymphocytes, the Kiel classification is based on a morphological approach and that of Lukes on a functional approach. These modern classifications should gradually replace the Rappaport classification, which predates the major developments of modern immunology. The Kiel nomenclature is described briefly. (12 refs)

79-0079 The Radiological Symptomatology of Primary Malignant Neoplasia of the Kidney. (Ita) Musumeci, R. (Istituto Nazionale Tumori, 1 via Venezian, I-20133 Milan, Italy); Botturi, M. *Radiol Med (Torino)* 64(6): 753-768; 1978.

The radiological symptoms of primary tumors of the kidney are reviewed. Renal cell carcinoma, accounting for 85% of all primary malignant tumors of the kidney, affects men and women in equal ratio, mostly in the sixth and seventh decades of life. Renal sarcoma is rare; it may originate from the capsule, parenchyma or cavity. Wilms' tumors account for about 6% of all renal tumors, and they are bilateral in about 10% of all cases. It affects boys and girls in equal ratio, usually during the third and fourth years of life. In an autopsy series, the incidence of malignant lymphoma of the kidney was 13% in lymphogranulomatosis, 33% in non-Hodgkin lymphoma, and 63% in lymphocytic lymphoma with bone marrow involvement. (48 refs)

79-0080 Radiological Study of Prostate Diseases. (Ita) Belli, I. (Servizio di Radiologia, Ospedale di Circolo di Varese, 57 Viale Borri, I-21100 Varese, Italy); Porro, R. C.; Del Favero, C.; Nascimbene, C.; Tenti, L. *Radiol Med (Torino)* 64(6): 769-784; 1978.

The radiological aspects of diseases of the prostate gland are reviewed. Prostatic carcinoma is fairly common; its incidence is higher than that of carcinoma of the stomach and colon. About 20% of old men are believed to have asymptomatic prostatic carcinoma. Contrary to prostatic hypertrophy, prostate carcinoma originates mostly from the posterointerior portion of the gland, and its proliferation is atypical. Two forms of prostatic carcinoma can be distinguished: (1) a fairly small neoplasia with early bone metastases, and (2) locally spreading carcinoma with progressive invasion of the urethra and urinary bladder. (36 refs)

79-0081 Diseases of the Paranasal Sinuses. Part 3: Tumors of the Paranasal Sinuses. (Ger) Draf, W.

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(Hals-Nasen-Ohren-Klinik, Universitat Mainz, Langenbeckstrasse 1, 6500 Mainz, W. Germany). *Fortschr Med* 96(47/48): 2355-2358; 1978.

The clinical, therapeutic, and diagnostic aspects of tumors of the paranasal sinuses are reviewed. Benign and malignant tumors of the paranasal sinuses are rare tumors; carcinomas at these sites account for about 0.2% of all carcinomas, and for about 3% of all carcinomas of the upper respiratory and digestive tracts. Their incidence is twice as high in men as in women, and they are rare in persons under the age of 35 yr. The incidence of sarcomas and adenomas is highest among young patients, while squamous-epithelial carcinomas usually occur in the fifth and sixth decades of life. The benign tumors include papillomas, adenomas, and mixed tumors of the epithelium; glioma, meningioma, neurofibroma, neurilemmoma, ganglioma, ganglioneuroma, paraganglioma, nevus, fibroma, myxoma, hemangioma, lymphangioma, chondroma, and lipoma of the connective tissues; osteoma, exostoses, osteoid osteoma, giant-cell tumors and cysts of the bones; and epithelial cysts, ameloblastoma, myxoma, fibroma, dentinoma, cementoma, cementifying fibroma and mixed tumors of the odontogenic tissues. The semimalignant tumors include inverted papilloma and leukoplakia of the epithelium; chordoma, plasmacytoma, teratoma, tumors of Rathke's pouch, hemangioendothelioma, hemangiopericytoma, Kaposi's sarcoma and Hand-Schuller-Christian disease of the connective tissue; and fibrous diseases. The malignant tumors of the paranasal sinuses are basal-cell carcinoma, squamous-epithelial carcinoma, lymphoepithelial carcinoma, spindle-cell carcinoma and adenocarcinoma of the epithelium, and Wegener's granulomatosis, fibrosarcoma, rhabdomyosarcoma, hemangioendotheliosarcoma, malignant lymphoma, myxosarcoma, reticulosarcoma, chondrosarcoma and Ewing's sarcoma of the connective tissues. (no refs)

- 79-0082 Woringer-Kolopp Disease.** (Fre) Revuz, J. (Service de Dermatologie, Hopital Henri-Mondor, F-94010 Creteil, France); Touraine, R. *Dermatologica* 157(6): 377-385; 1978.

Studies on the phenomenology and nosology of Woringer-Kolopp disease are reviewed. Woringer-Kolopp disease is a rare skin disease, affecting almost exclusively men, at practically any age. The disease is characterized by erythematous, slightly infiltrated lesions with round islets of normal skin and disruption of the stratum spinosum by dense epidermal infiltrate. The lesion develops in intact skin without preexisting "parapsoriasis en plaques." There are no visceral or lymph node lesions. Two forms are distinguished: a benign localized or regional form and a malignant disseminated type. A similar disseminated lesion, appearing on erythematous patches that are clinically and histologically similar to "parapsoriasis en plaque," is considered an ex-

tremely epidermotropic variant of mycosis fungoides. The examination of a new case supports the theory that Woringer-Kolopp disease is a proliferation of Merkel's cells. (20 refs)

- 79-0083 Papanicolaou Smear, Colposcopy and Cervical Cancer Precursors.** (Eng) Coppleson, M. (Dept. Gynaecology and Obstetrics, King George V Memorial Hosp., 139 Macquarie St., Sydney, New South Wales 2000, Australia). *Med J Aust* 2(7): 305-307; 1978.

The management of cervical cancer precursors based on exfoliative cytology and histologic examination has a major deficiency in that a lesion remains unseen. Colposcopy enables its rapid visualization and makes it possible to correlate the intensity of atypical changes with the corresponding histological changes. With a good colposcopy service, punch biopsy becomes the main method of diagnosis. Current approaches to the management of preclinical invasive carcinoma, carcinoma in situ, and dysplasia are discussed. (18 refs)

- 79-0084 Cancers Arising from Chronic Wounds, or the Hazards of Disturbed Healing (Report of 33 Cases).** (Fre) Abbes, M. (Service de Chirurgie, Centre Antoine Lacassagne, 36, Voie Romaine, 06054 Nice Cedex, France); Barety, M. *Ann Chir Plast* 23(2): 80-85; 1978.

Thirty-three patients (21 men and 12 women) developed cancer from chronic wounds caused by trauma and other factors. Most patients were aged > 50 yr at the time of diagnosis. The chronic wounds included burns, infections, damage to nerves, mechanical trauma, and radiogenic lesions. The latent period ranged from 6 mo to 50 yr. The av latent period was 29 yr for burns, 25 yr for chronic infection, 25 yr for nerve damage, 17 yr for mechanical trauma, and 13 yr for radiogenic lesions. Squamous cell carcinoma was diagnosed in 18 patients, basal cell carcinoma in 13, and rhabdomyosarcoma and spindle-cell sarcoma in 1 each. Lymph node metastases were found in two patients. (32 refs)

- 79-0085 The Vascular Endothelium--Pathobiologic Significance. A Review.** (Eng) Thorgeirsson, G. (Inst. Pathology, Case Western Reserve Univ., Cleveland, OH, 44106); Robertson, A. L. *Am J Pathol* 93(3): 801-848; 1978.

Diseases in which physiopathologic alterations of endothelial tissue may play key roles, including inflammation, immune disorders, and vascular neoplasia and metastasis, are re-

viewed. Vascular endothelium can give rise to benign and malignant hemangioendotheliomas, but it more frequently assumes a role in the metastatic spread of other tumors. (271 refs)

- 79-0086 Cell Kinetics: Summary of Recent Findings in Studies of Gastrointestinal Disease in Man.** (Eng) Lipkin, M. (Memorial Sloan-Kettering Cancer Center, New York, NY, 10021). *J Environ Pathol and Toxicol* 2(1): 9-11; 1978.

Recent findings of studies of human gastrointestinal diseases are reviewed with respect to using cytokinetic measurements to identify individuals and population groups at risk. In several diseases associated with increased frequencies of neoplasia in the gastrointestinal tract, as well as in other organs of man, cells lose their ability to repress DNA synthesis before the development of invasive malignancy. Studies of carcinogenesis mechanisms in populations at high risk for colon cancer should include identification of the abnormal cellular and related characteristics that are present. (22 refs)

- 79-0087 Carcinogenesis due to Air Pollution.** (Ita) Tar-
sitani, G. (No affiliation given). *Nuovi Ann Ig
Microbiol* 28(5): 301-306; 1977.

A review of epidemiological studies shows that some indicate that there is a correlation between cancer and air pollution but others do not. Epidemiological studies in this area should be coordinated. (10 refs)

- 79-0088 Adipose Tissue and Aetiology of Breast Cancer (Letter to Editor).** (Eng) Petrakis, N. L. (Dept. Epidemiology and International Health, Univ. California, San Francisco, CA, 94143); Ernster, V. L. *Lancet* 2(8097): 1001; 1978.

The hypothesis that women with abundant breast adipose tissue are predisposed to the development of breast cancer is refuted. Following release from breast fat cells, carcinogens first reach the venules and lymphatics surrounding the fat cells and then enter the circulation. Upon recirculation to the breast, carcinogens could be taken up directly and secreted by the alveolar epithelial cells. There is no need to believe that an excess of breast fat would be more hazardous to breast epithelium than any other more distantly located fat deposits,

such as sc fat and the omentum, that store fat-soluble substances. (2 refs)

- 79-0089 Early Nutrition, Growth, Disease, and Human Longevity.** (Eng) Stini, W. A. (Dept. Anthropology, Univ. Arizona, Tucson, AZ, 85721). *Nutr and Cancer* 1(1): 31-39; 1978.

The size of the human body has increased in the last 100 yr, and maximization of growth may predispose the individual to certain degenerative conditions, including cancer. Animal experiments have shown that restricted feeding is correlated with increased longevity and reduced tumor incidence. Indications of similar effects of diet on cancer incidence in humans are given. On a statistical basis alone, a greater number of cells, associated with accelerated growth, may increase the probability of malignant transformation. Cancers of the breast and colon are more prevalent in well-nourished than in undernourished populations. Both height and wt are positively correlated with cancer incidence in postmenopausal women. Increased estrogen synthesis and storage in adipose tissue may be implicated in this correlation. Japanese immigrants to Hawaii experienced a rapid increase in bowel cancer incidence simultaneous with a substantial increase in av body size. Some investigators argue that increased beef consumption is the underlying cause, and others attribute the correlation to an overall increase in fat consumption. However, not all researchers are convinced that correlations between fat intake per se and colon and breast cancer are truly significant. The mechanisms by which dietary factors influence cancer incidence probably involve the immune system. One hypothesis is that early nutritional deprivation may keep the immune system "young" longer, permitting it to retain competence to react against neoplasms later in life. Nutritional deprivation may lower the likelihood of autoimmune reactions in later years. (74 refs)

- 79-0090 Diet and Nutrition in Cancer Causation.** (Eng) Gori, G. B. (NCI, Bethesda, MD, 20014). *Nutr and Cancer* 1(1): 5-8; 1978.

Epidemiological and laboratory data on the relationship of dietary components to the incidence of certain forms of cancer are reviewed. Diet functions as an etiologic factor distinct from dietary contaminants and from genetic and environmental factors. Correlations between cancer incidence and dietary habits have been shown in studies of migrant populations, high- and low-cancer incidence populations, and special (ie, religious or ethnic) populations. (48 refs)

- 79-0091 The Role of Nutrition in the Control of Cancer.** (Eng) Navarro, M. D. (Univ. Santo Tomas Res. Center, Manila, Philippines). *Acta Manilana Series A* 17(27): 3-15; 1978.

The role of diet in carcinogenesis is discussed. It is suggested that persons who eat little or no meat, but consume large amounts of vegetables, fruits, and their seeds, are less subject to cancer. It is felt that the presence of fruits and vegetables rich in vitamin B17 and nitrilosides are responsible for this phenomenon. (19 refs)

- 79-0092 The Epidemiology of Endometrial Cancer.** (Eng) Kloppe, A. (Dept. Obstetrics and Gynecology, Univ. Aberdeen, Aberdeen, Scotland); Farr, V. In: *Front Horm Res* 5: 89-100; 1978.

A review of the epidemiology of endometrial cancer is presented that attributes the increase in endometrial cancer to the increasing use of estrogen replacement therapy in menopausal women. Risk factors include obesity, diabetes, and age. In the postmenopausal woman, estrogens are produced by the peripheral conversion in body fat of androstenedione to estrone. The more fat, the more estrone, and the more estrone, the greater the liability to cancer. One contradiction to this thesis is that estrogen administration acts independently of obesity in causing endometrial carcinoma. The association of diabetes with carcinoma of the endometrium is not as strong as that of obesity but it is probably real. Hypertension, affluence, and genetic factors have also been considered as risk factors but the evidence is not convincing. Examination of the role of endogenous estrogen in endometrial carcinoma implicates the action of estrogen unopposed by progesterone and possibly the prolonged action of estrogen but not the action of high estrogen levels. All evidence is against one endogenous estrogen, estrone. With regard to exogenous estrogens, the evidence points to estrone sulfate and conjugated equine estrogens, to synthetic estrogens such as stilbestrol or ethynyl estradiol or to nonsteroidal estrogens in the genesis of endometrial cancer. There is no evidence to implicate the natural steroids estradiol-17 β and estriol. (28 refs)

- 79-0093 Hodgkin's Disease.** (Eng) Izak, G. (Dept. Hematology, Hadassah Univ. Hosp. and Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel). *Isr J Med Sci* 14(10): 1010-1013; 1978.

The impaired cellular immunity of patients with Hodgkin's Disease (HD) and its possible relationship to the etiology of the disease and to the susceptibility of the patients to infections are reviewed. A viral infection could be partly responsi-

ble for the T-cell defect in HD patients, but no meaningful conclusions can be drawn from the available data. The prevalence of herpes zoster in HD exceeds substantially that observed in non-Hodgkin's lymphoma and in other conditions associated with impaired immune defense mechanisms. (37 refs)

- 79-0094 Disentangling Kaposi's Sarcoma (Letter to Editor).** (Eng) Hutt, M. S. (Geographical Pathology Unit, Dept. Morbid Anatomy, St. Thomas's Hosp. Medical Sch., London SE1, England); Bland, J. M. *Br Med J* 2(6150): 1498; 1978.

According to a series of papers from Malawi, Uganda, Tanzania, and Zambia, in which the distribution and clinical features of Kaposi's sarcoma were reviewed, there is no evidence to suggest that the tumor is related to the endemicity of malaria or to any other specific parasitic disease. It is likely that endogenous, possibly hormonal, factors play an increasing role with age in determining susceptibility or resistance to the causative agents. (4 refs)

- 79-0095 Membrane Changes During Neoplastic Transformation.** (Eng) Franke, W. W. (Inst. Experimental Pathology, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280 6900 Heidelberg, W. Germany). In: *Neoplastic Transformation: Mechanisms and Consequences. Proceedings of a Meeting held by the Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences in Berlin, May 9-13, 1977.* Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences (Berlin, W. Germany): 314 pp.; 181-195; 1977.

Many recent studies have focused on delineating structural and biochemical abnormalities in membranes of transformed or malignant cells. It is now generally accepted that the unit membrane structure of a malignant cell cannot be distinguished from its counterpart in a normal cell. Attempts to prove that malignant cells exhibit differences in characteristics such as intercellular coupling (gap junctions, tight junctions), lipid composition, and microviscosity have at best been inconsistent. Convincing evidence has accumulated, however, to substantiate a correlation between malignancy and two biochemical alterations in cell membranes; (1) changes in the glycolipid pattern and in the activities of the corresponding glycosyltransferases and (2) increases in the sialic acid content of some fucose-containing glycopeptides. These changes appear to be widespread and consistent and, for this reason, may be regarded as general phenomena associated with neoplasia. (55 refs)

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79-0096 A Quantitative Approach to Structure Activity Correlation in Chemical Mutagenesis-Preliminary Studies in the Ames' *Salmonella*/Microsome Assay Systems. (Eng) Johnson, H. L. (SRI International, Menlo Park, CA, 94025); Sigman, C. C. In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977*. Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 105-111; 1978.

A system for the quantitative analysis of the effects of chemical structure, properties, and reactivity on chemical mutagenesis is described together with its applications in predicting the mutagenicity of untested compounds. A computer model is derived whereby mutagenic activity is mathematically related to a combination of various chemical parameters (chemical composition, size, shape, reactivity, etc) and values that reflect the contribution of the associated parameter to activity. The system used for determination of activity involves the induction of revertants in the Ames *Salmonella typhimurium* histidine auxotroph assay. Activity is expressed as the concentration at which half-max activity is observed, and the ratio of the activity of the experimental compound to that of a chemical standard tested in the same study. After parameters and activities are chosen, the computer system PROPHET runs multiple regression analyses. The potential predictive value of the system is illustrated by the results of a preliminary Ames test with a group of aromatic amines. (6 refs)

79-0097 Ab Initio and Nonempirical MODPOT/VRDDO Calculations on Drugs, Carcinogens, Suspected Teratogens, and Biomolecules. (Eng) Kaufman, J. J. (Dept. Anesthesiology, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205); Popkie, H. E.; Preston, H. J. *Int J Quant Chem Quant Biol Symp* (5): 201-218; 1978.

An overview of recent nonempirical ab initio MODPOT/VRDDO calculations on a variety of drugs, nucleic acid constituents, normal neurotransmitters and their metabolites, carcinogens and their activated metabolites, suspected teratogens, and the attack of carcinogens on DNA constituents is presented. The intrinsic tractability and timing of the calculations as a function of the size and geometry of a variety of biomolecules is emphasized. The MODPOT/VRDDO method incorporates two desirable options into fast ab initio Gaussian programs: MODPOT-ab initio effective core model potentials and a charge-conserving integral prescreen-

ing approximation, which was named VRDDO (variable retention of diatomic differential overlap). For orbital energies and population analyses, the MODPOT/VRDDO results agree to essentially three decimal places with those of completely ab initio calculations with the same valence atomic basis set. Some molecular electrostatic potential contour maps, which were generated from previously calculated ab initio wave functions, are discussed. These maps allow a cogent comparison of pharmacophores in molecules that exert a similar pharmacological effect by the same mechanism. An example of such a comparison is that of morphine and nalorphine. (45 refs)

79-0098 Conformational Analysis in QSAR Investigations. (Eng) Hopfinger, A. J. (Case Western Reserve Univ., Cleveland, OH). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977*. Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 74-81; 1978.

An attempt was made to correlate the biological activities and molecular features of a series of compounds using an automated quantitative structure-activity relationship (QSAR) method developed from two existing methods. The additive molecular thermodynamic model (linear free energy model) and conformational analysis (molecular orbital theory) were merged through solvent-dependent empirical energy functions. Molecular energy calculations involved functions such as dispersion, electrostatic interactions, hydrogen bonding, valence bond interactions, solute-solvent interactions, and intrinsic torsional potential. The CAMSEQ computer system was used for the calculations. Potential anticancer agents, the Baker triazines, were studied by QSAR in an in vitro dihydrofolate reductase inhibition activity assay. The statistical wts of the triazines correlated with their in vitro inhibition activity. Newly developed QSAR techniques are being used that employ molecular structure calculations to construct models of interactions between carcinogens and DNA. It is hoped that further calculations will shed light on the sites of physical interaction with DNA and indicate whether the physical interactions lead to chemical interactions. (15 refs)

79-0099 Pattern Recognition Methods. (Eng) Jurs, P. C. (Pennsylvania State Univ., University Park, PA 16802). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administra-*

tion Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977. Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 88-94; 1978.

The evaluation of structure-activity relations (QSAR) through the use of pattern recognition and chemical structure information-handling techniques is described. QSAR information may be useful in predicting the classification of untested compounds, based on discriminant functions and classification of tested compounds. The foundation of the structure-activity study is the modular computer system "ADAPT". Analysis begins with molecular structure input modules that are designed around square matrices whose main diagonals code for atom types and off-diagonals for bond types. Next, descriptors (physicochemical or calculated: topological and geometrical) must be generated from internal storage. These descriptors cover parameters such as partition coefficients, lipophilicity, steric constants, atom and bond fragments, substructures, and sizes and shapes of molecules. Finally, pattern recognition uses this data to congregate compounds with common properties into "limited regions of space", mathematically separable on a linear decision surface. Although this system has not yet been used in mutagenesis or carcinogenesis studies, preliminary studies on compounds associated with olfactory toxicity detection demonstrated a predictive ability of 92%. (21 refs)

- 79-0100 Reticulum Cell Sarcomas as Sequelae of CO₂-Treatment of Normal Tissue.** (Eng) Goldsmith, A. E. (Natl. Cancer Cytology Center, Melville, NY); Ryan, G. F. In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 971-987; 1977.

The effects of abnormal CO₂ concentrations on various tissues were determined by exposing skin, mammary gland, and lymph node tissue from BALB/c, CBA, or Swiss albino mice in vitro to 45% CO₂ in air and transplanting these tissues as isografts and autografts. The incidence of malignant lymphomas in all CO₂-treated graft recipients, even autograft recipients, was higher than the spontaneous incidence in that strain. Irrespective of pretransplantation treatment of the graft or tissue type grafted, all inbred (BALB/c and CBA) recipients of isografts had a high lymphoma incidence (20%-61%). The noninbred Swiss mice had a spontaneous incidence of 8% at age 5-13 mo; the incidence increased above this age. In contrast to the inbred strains and possibly due to their higher spontaneous incidence, the occurrence of lymphoma in the Swiss mice rose to 63%-88% in all graft recipients, irrespective of pretransplantation treatment, type of graft, or tissue type grafted. Only the CO₂-treated autograft recipients had a high lymphoma incidence in BALB/c mice (33%); grafts exposed to air alone elicited no lymphomas in

their hosts. The appearance in graft recipients of significant numbers of lesions associated with altered immunological status, particularly glomerular lesions and myocarditis, pointed to an involvement of immunological mechanisms in lymphoma formation. Increased lymphoid activity in T- and B-cell lines was observed in the spleens of lymphoma-bearing mice, contrasting sharply with the decrease in nodal activity. Findings in non-lymphoma-bearing controls were the reverse. An interrelationship appeared between T-cell hyperplasia and B-cell atrophy. The highest incidences of both occurred in the experimental spleens, the lowest in the nodes. However, moderate incidences of both occurred in control spleens and nodes. Autoimmune-type mechanisms in some tumor productions were suggested by the development of lymphomas following CO₂ exposure in utero and of pulmonary adenocarcinomas (33%) and lymphomas following direct introduction of gaseous CO₂ in the subphrenic area. The chronic abnormal accumulation of CO₂ in the tissues may so alter the microenvironment of cells as to cause the formation of abnormal immunogenic cells or other factors with carcinogenic properties. (31 refs)

- 79-0101 Cytogenetic Effects of Inhaled Ozone.** (Eng) Tice, R. R. (Medical Dept., Brookhaven Natl. Lab., Upton, NY, 11973); Bender, M. A.; Ivett, J. L.; Drew, R. T. *Mutat Res* 58(2/3): 293-304; 1978.

Cultured lymphocytes from Chinese hamsters that had inhaled ozone were examined for chromosomal aberrations, sister-chromatid exchanges (SCE), and cell-replication rates. The hamsters were exposed to an av ozone concentration of 0.43 ppm for 5 hr, for a total of 2.15 ppm-hr. Female mice were exposed to 2.0 ppm for 6 hr, or 12 ppm-hr. Blood was obtained either immediately or 7 or 14 days after exposure. No increases in chromosome-type aberrations were observed at any sampling time. At later sampling times, there were increases in the levels of aberrations of the chromatid-type. No increase in the levels of any chromosomal aberration type was seen in parallel direct bone-marrow preparations. SCE levels and cell-replication rates, determined in both the Chinese hamster peripheral lymphocyte cultures and in bone-marrow samples from the treated mice, failed to show any ozone-induced changes. These results are in contrast to those of a previous study in which substantial frequencies of chromosome deletions, rings, and dicentric were reported in cultures of blood cells after ozone exposures of 1.5 ppm-hr. The increases seen in the number of chromatid-type aberrations are similar to those reported in cultures of blood samples obtained from human subjects one or more weeks after exposure to 5 ppm-hr ozone. These results indicate that inhalation of ozone at the levels to which populations are currently exposed, and for the times such levels persist, is unlikely to present an appreciable genetic hazard. (34 refs)

- 79-0102 Arsenic and Cancer: Effects of Joint Administration of Arsenite and Selenite on the Genesis**

of Mammary Adenocarcinoma in Inbred Female C₃H/St Mice. (Eng) Schrauzer, G. N. (Dept. Chemistry, Univ. California at San Diego, Revelle Coll., La Jolla, CA, 92093); White, D. A.; McGinness, J. E.; Schneider, C. J.; Bell, L. J. *Bioorg Chem* 9(3): 245-253; 1978.

The effects of low doses of arsenic (as arsenite: 2 ppm in drinking water) and/or selenium (as selenite: 2 ppm in drinking water) on the incidence of spontaneous mammary adenocarcinomas in female inbred C₃H/St mice was investigated. At 22 mo, the spontaneous tumor incidence in the four experimental groups (controls, As, As + Se, Se) was 12/30, 10/30, 18/30, and 5/30, indicating that As abolished the anticarcinogenic effect of Se. The age at tumor onset in the four groups was 4.5, 9, 8, and 16 mo, respectively. Arsenite increased the tumor growth rates significantly and raised the incidence of multiple tumors (17%, 40%, 28%, and 0%, respectively). The tumor growth rates in the As + Se group were also increased, but the incidence of multiple tumors was significantly lower than that in the As group. The latter finding demonstrates that Se diminished some of the deleterious effects of As. (20 refs)

79-0103 Light and Electron Microscope Studies of the Rat Digestive Tract Following Prolonged and Short-Term Ingestion of Chrysotile Asbestos. (Eng) Jacobs, R. (Dept. Biochemistry, Univ. Coll., Cardiff, Wales); Humphrys, J.; Dodgson, K. S.; Richards, R. J. *Br J Exp Pathol* 59: 443-453; 1978.

The effects of feeding MRC hooded rats 0.5 or 50 mg chrysotile asbestos daily for 1 wk or 14 mo on the cells of the gastrointestinal tract were determined by light and electron microscopy. Light microscopy showed that the ileum underwent the most marked changes. Short- or long-term feeding at either dose resulted in general disorganization of the ileum: the regularity of the tips of the villi was absent, and vacuolization in the mucosal epithelia and the connective tissue villus core of the lamina propria was marked. In some cases, the mucosal epithelial cells were separated from the villus core along the line of the thin basal lamina. The rectal and colonic lumens contained clumps of nuclei and blue-staining mucinous material, but the esophagus, stomach, and cecum had a basically normal appearance. Electron microscopy of the ileum of rats receiving 50 mg/kg asbestos for 14 mo confirmed the light microscope findings and showed various changes in the mucosal lining cells that were consistent with a mineral-induced cytotoxicity. Mucosal absorptive cells were detached along the line of the intercellular membranes, with loss of the tight junctional complexes, thus creating enlarged intercellular spaces. Loss of the brush border, vacuolization along intercellular membranes or in the cells themselves, and abnormal blebbing of the surface microvilli were also noted. Colonic tissue showed similar changes, and both microvilli and goblet cells stained very densely. The lumen was filled with mucinous cell debris and bacteria that adhered to the cell surface even after repeated washing. It appears that

chrysotile asbestos-induced toxicity is specific for certain regions of the rat gastrointestinal tract. (13 refs)

79-0104 Short-Term Asbestos Exposure and Delayed Cancer Risk. (Eng) Seidman, H. (American Cancer Society, 777 Third Ave., New York, NY, 10017); Lillis, R.; Selikoff, I. J. In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 943-960; 1977.

Lung cancer mortality was examined in 914 white men who had worked for short periods (585 for <1 yr) in an amosite asbestos factory during World War II and who were followed for 30 yr, beginning in 1943. Mortality data for each of the 30 yr were compared with age-specific death rates for white men in New Jersey during 1941-1974. Of the 135 verified cancer deaths in the asbestos workers, 76 were due to lung cancer. Among the 65 men who worked <1 mo, no lung cancer death occurred until 25 yr postexposure. With longer asbestos exposure (ie., 2, 3, 6, mo), the cancer risk became greater; and in men who worked 2+ yr, the observed number of lung cancer deaths 10-29 yr after onset of work was 33 vs 4.00 expected. Lung cancer alone did not account for the excess mortality in the 2+ yr group, in which the number of deaths from all causes was 113 vs 73.45 expected and the number of deaths from all cancers was 47 vs 14.89 expected. It is emphasized that longer employment resulted in cancer after shorter postexposure observation. (17 refs)

79-0105 Malignant Mesothelioma of the Pleura in Barrow-in-Furness. (Eng) Edge, J. R. (North Lonsdale Hosp., Barrow-in-Furness, Cumbria LA14 2JD, England); Choudhury, S. L. *Thorax* 33(1): 26-30; 1978.

The occurrence of malignant pleural mesothelioma among 47 men and 3 women living in Barrow-in-Furness, England (a town in which ship construction is the major industry), is discussed. All cases were diagnosed between 1966 and 1976, and all patients but one were known to have been exposed to asbestos dust (all 47 men and 1 woman had worked in the shipyard; 1 woman was married to a shipyard plumber). The histological picture was predominantly mixed in 24 patients, tubopapillary in 15, and undifferentiated in 11. Asbestos fiber counts in the lungs exceeded acceptable levels for the general population in 18/20 patients examined, and 13/16 patients examined had asbestos bodies in the lungs. Electron microscopy showed that the predominant fiber was crocidolite and that the number of fibers present was always small compared with the usual number in pulmonary asbestosis. Forty-seven patients presented with a massive pleural effusion, and pleural plaques were diagnosed on the side opposite the tumor in 30 cases. Distal metastases were never recognized clinical-

ly, but were found in 25/47 patients at necropsy. Diagnostically, cytological examination of the pleural fluid was as useful as needle biopsy. (19 refs)

- 79-0106 Studies on Lead and Cadmium Contamination from Drying of Cereals by Gases from Burning Fuel.** (Ger) Woggon, H. (Zentralinstitut für Ernährung, Arthur-Scheunert-Allee 114/116, DDR-1505 Bergholz-Rehbrücke, E. Germany); Malkus, Z. *Nahrung* 22(7): 647-654; 1978.

Two methods for determination of Cd and Pb in cereals were used to study possible contamination if diesel oil or brown coal is used as the fuel for the drying of cereal. Direct drying using exhaust gas from burning fuel was found to add no significant amount of Cd or Pb to cereal; however, because earlier studies have shown increases in 3,4-benzpyrene and other polyaromatic compounds, it is recommended that this type of drying be abandoned. The av levels found after drying were: 0.052 mg Cd/kg (suggested tolerance 0.10 mg/kg) and 0.36 mg Pb/kg (suggested tolerance 0.5 mg/kg). Direct and indirect (no contact between cereal and exhaust gases from the burning fuel) drying gave similar results. Direct inverse polarography (IP) and indirect IP (extraction with dithizone and re-extraction with HCl) were used for determination of Pb and Cd. Direct IP was found preferable for small amounts of Cd and for all levels of Pb. Recoveries of known amounts of Cd or Pb ranged from 76%-133%. Both methods seem suitable for studies of Pb or Cd contents of cereal products. (6 refs)

- 79-0107 Chromosome Studies on Blood Lymphocytes of Men Occupationally Exposed to Cadmium.** (Eng) O'Riordan, M. L. (MRC Clinical, Population Cytogenetics Unit., Western General Hosp., Crewe Road, Edinburgh, Scotland); Hughes, E. G.; Evans, H. J. *Mutat Res* 58(2/3): 305-311; 1978.

Chromosome studies were carried out on peripheral blood lymphocytes from 40 men occupationally exposed to cadmium salts for periods up to 34 yr and from 13 on-site controls. The mean Cd blood level in the exposed group was 1.95 $\mu\text{g}/100\text{ ml}$ (range <0.2-14.0 $\mu\text{g}/100\text{ ml}$), whereas eight controls had levels <0.2 $\mu\text{g}/100\text{ ml}$ and the remaining five levels between 0.6 to 2.9 $\mu\text{g}/100\text{ ml}$. Although four chromatid interchanges were observed in 3,740 cells from the exposed workers and none in the 1,243 cells from controls, there was no significant difference in aberration frequency between the two groups. Three of the chromatid interchanges in the exposed workers involved both homologs of chromosome 9, and the fourth involved two F group (19-20) chromosomes. The extent of chromosome damage detected in an individual worker did not correlate with his length or degree of exposure to Cd or with his blood Cd level. Possible reasons for contrasting findings on the chromosome-damaging effects of

Cd in other published reports are discussed, and the possibility that heavy metals might act synergistically to enhance the mutagenicity of other compounds present in the environment is considered. (24 refs)

- 79-0108 Comparative Studies of Chromosomal Aberration and Mutagenicity of Trivalent and Hexavalent Chromium.** (Eng) Nakamuro, K. (Dept. Hygienic Chemistry and Microbiology, Natl. Inst. Hygienic Sciences, Kamiyoga, Setagaya-ku, Tokyo 158, Japan); Yoshikawa, K.; Sayato, Y.; Kurata, H. *Mutat Res* 58(2/3): 175-181; 1978.

The effects of two hexavalent and three trivalent chromium compounds on the incidence of chromosome aberrations in leukocytes from a healthy man on the results of a recombination assay (rec-assay) with wild-type *Bacillus subtilis* strain 17A and its recombination-deficient (rec-) derivative 45T, and on the results of a mutation assay for arginine reversion with *Escherichia coli* strain Hs30R were investigated. When leukocytes were exposed to concentrations of chromium compounds near natural levels, the frequency of aberrations, including chromosome breaks and exchanges, as well as the total number of aberrations both increased with increasing dose. In total yield of aberrations (on an equimolar basis) the efficiency in inducing chromosomal aberrations was $\text{K}_2\text{Cr}_2\text{O}_7 > \text{K}_2\text{CrO}_4 > \text{Cr}(\text{CH}_3\text{COO})_3 > \text{Cr}(\text{NO}_3)_3, \text{CrCl}_3$. Rec-assay effects were marked, as indicated by differences in the size of the inhibition zone from 2 to 9 mm. The hierarchy of DNA-damaging activity was similar to the efficiency of inducing chromosomal aberrations; $\text{K}_2\text{Cr}_2\text{O}_7$ and K_2CrO_4 were the most active and induced a dose-dependent effect. Three compounds exhibited mutagenic activity in the hierarchy $\text{K}_2\text{Cr}_2\text{O}_7 > \text{K}_2\text{CrO}_4 > \text{Cr}(\text{CH}_3\text{COO})_3$; cell survival was inversely related and frequency of reversion directly related to dose in each case. The two hexavalent chromium compounds were consistently more successful in producing aberrations than were the three trivalent compounds. The evidence supports the hypothesis that DNA damage induced as chromosomal aberrations is related to the rec-effect and mutagenicity. (13 refs)

- 79-0109 The Mutagenicity of Dichloroacetaldehyde.** (Eng) Lofroth, G. (Wallenberg Lab., Univ. Stockholm, S-106 91 Stockholm, Sweden). *Z Naturforsch C* 33(9/10): 783-785; 1978.

The Salmonella/microsome test showed that 2,2-dichloroacetaldehyde, a presumed metabolite of the insecticides dichlorvos and trichlorphon, was more mutagenic [58 revertants/micromole (μmol)] than the established mutagen dichlorvos [17 revertants/ μmol] but approx one-tenth as mutagenic as chloroacetaldehyde [515 revertants/ μmol]. (20 refs)

- 79-0110 On the Detection of Volatile Liquid Mutagens with Bacteria: Experiments with Dichlorvos and Epichlorhydrin.** (Eng) Bridges, B. A. (M.R.C. Cell Mutation Unit, Univ. Sussex, Falmer, Brighton BN1 9QG, England). *Mutat Res* 54(3): 367-371; 1978.

Optimal conditions for detecting volatile liquid mutagens by means of bacteria were studied using dichlorvos and epichlorhydrin. The bacteria were usually suspended for 1 hr in a solution of the mutagen in buffer then plated on a medium that would permit expression of induced mutants. The modified fluctuation medium helps ensure that the mutagen is present for as long as possible when the maximum number of cells are available for exposure. The possibility of loss of mutagen through evaporation was avoided by incorporation of a relatively stable mutagen into semi-enriched plates. In the case of dichlorvos the sensitivity was not as great when the mutagen was added to the agar as when the mutagen was allowed to vaporize from a filter paper pad or watch-glass in the jar. Sensitivity was further enhanced by using a plasmid-containing strain of *Escherichia coli* (such as CM 881) and by using glass rather than polystyrene plates. Thus detection of dichlorvos concentrations down to at least 0.1 µg/ml agar was possible. With epichlorhydrin, concentrations down to 1.25 µg/ml air were detectable using *Salmonella typhimurium* TA100 on the surface of agar in glass plates sealed in air-tight steel or glass jars. (8 refs)

- 79-0111 The Balkan Endemic Nephropathy and Cancer of the Urinary Tract.** (Eng) Markovic, B. (Medical Center, Gnjilane, Yugoslavia); Lebedev, S. In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp; 1179-1189; 1977.

The development of malignant urothelial tumors in Balkan endemic nephropathy, a chronic kidney disease caused by drinking water containing silicate minerals and heavy blastogenic metals, was studied experimentally in mice. The animals were given 50 mg/liter quartz and 100 mg/liter quartzite in the drinking water. The quartzite contained Ni, Cr, Al, Mg, Ba, Fe, Ca, and Ti. After 2 mo, the animals lost wt and developed polydipsia and polyuria. Every fourth month, quartzite was discontinued during the first 15 days; during this time the water contained only quartz. During the next 15 days, the mice were given pure water only. Chronic interstitial nephritis and urinary tract tumors were found simultaneously after 12 mo. In the kidney, focal periglomerular inflammatory-proliferative infiltration led to fibrotic thickening of the Bowman's capsule. Sclerosis and hyalinization occurred in the glomeruli. The parenchymal lesions included dystrophy, hypertrophy, atrophy, or necrosis. Tubules were most often found to be dystrophic or hypertrophic in their proximal convoluted areas. Ultrastructural examination of

kidney samples taken at 9-12 mo showed focal mesenchymal proliferation of the interstice of the renal cortex and medulla with multiplication of collagen fibers. The glomerular changes were focal. Fine spherical granular osmiophilic inclusions, 0.1-0.5 µ in diameter, occurred in the mitochondria of the proximal tubular epithelium in all samples studied. Urothelial neoplastic proliferation occurred in over half the treated animals. (9 refs)

- 79-0112 Sister-Chromatid Exchange Induction by Sodium Selenite: Dependence on the Presence of Red Blood Cells or Red Blood Cell Lysate.** (Eng) Ray, J. H. (Graduate Sch. Biomedical Sciences, Medical Genetics Center, Univ. Texas Health Science Center, P. O. Box 20334, Astrodome Station, Houston, TX, 77025); Altenburg, L. C. *Mutat Res* 54(3): 343-354; 1978.

Induction of sister-chromatid exchange (SCE) by sodium selenite (Na_2SeO_3) was studied in short- and long-term cell cultures. Concentrations of Na_2SeO_3 (7.90×10^{-6} M and greater) that produced elevated SCE frequencies in whole-blood cultures did not increase SCE frequencies above control levels in Ficoll-Hypaque-purified lymphocyte cultures. However, whole blood and purified lymphocyte cultures were equally sensitive to SCE induction by methyl methanesulfonate, ethyl methanesulfonate, and N-hydroxy-2-acetylaminofluorene. Addition of RBC or RBC lysate, but not RBC ghosts, plus Na_2SeO_3 to purified lymphocyte cultures increased the SCE frequency to a value comparable to that observed in whole blood cultures exposed to the same Na_2SeO_3 concentration. Na_2SeO_3 alone did not increase the SCE frequency in xeroderma pigmentosum (XP12RO) or human lymphoblastoid cell cultures, whereas the SCE frequency in both cultures was significantly increased after treatment with Na_2SeO_3 plus RBC lysate. Na_2SeO_3 was equally toxic to the cultured cells in the presence and absence of RBC lysate. (39 refs)

- 79-0113 Oxidation of Inactive Trivalent Chromium to the Mutagenic Hexavalent Form.** (Eng) Petrilli, F. L. (Inst. Hygiene, Univ. Genoa, Via Pastore 1, 16132, Genoa, Italy); De Flora, S. *Mutat Res* 58(2/3): 167-173; 1978.

In plate-incorporation tests, soluble trivalent chromium compounds (chromium potassium sulfate, chromium nitrate, chromium chloride, neochromium and chromium alum) were inactive for *Salmonella typhimurium* TA100, even at milligram amounts per plate. No mutagenic effect could be detected in the absence or in the presence of rat liver, lung, or muscle microsomal fractions; rat muscle mitochondria (with or without ATP); oxidized glutathione; or human serum, plasma, or RBC lysates. Conversely, the addition of a strongly oxidizing agent (potassium permanganate) resulted in toxic effects in plates incorporating more than 40-80 µg of compounds and elicited a dose-effect mutagenic re-

sponse at 10-40 μg per plate. These effects could be ascribed to oxidation of chromium from the trivalent to the active hexavalent state. Insoluble chromite, assayed in the spot test, was spontaneously mutagenic, owing to contamination of the industrial product with hexavalent chromium. These results may be useful in interpreting the findings of carcinogenicity tests and in predicting the health hazards linked to chromium. (20 refs)

- 79-0114 Induction of Monozygotic Twinning in the Mouse.** (Eng) Kaufman, M. H. (Dept. Anatomy, Univ. Cambridge, Cambridge, England); O'Shea, K. S. *Nature* 276(5689): 707-708; 1978.

The teratogenicity of vincristine sulfate was investigated during the early stages of embryogenesis in CFLP mice. Mice were injected ip with 0.3 mg/kg vincristine sulfate on the 6th, 7th, or 8th day of gestation. A low incidence of gross anomalies (ie, a hindbrain appearing flattened, apparently caused by collapse of the region overlying the fourth ventricle) was observed in fetuses on days 10 and 12 of gestation. A high incidence of fetuses with abnormal heads was observed in the population of fetuses isolated from females treated on the 7th day (6.2%) compared with those isolated from females treated on the 6th (2.6%) and 8th (2.6%) day of gestation. Four sets of twins, one pair of which was conjoined, were observed when females were treated on the 7th day of pregnancy. Of five females autopsied on the 10th day, three each had one set of twins, and a single pair of conjoined twins (janiceps type) was isolated from one of four females autopsied on the 12th day of gestation. One additional set of twins was obtained from a female treated on the 8th day. The present study is unique in that an experimental method of inducing a low but significant incidence of identical twinning in a mammal is reported. (11 refs)

- 79-0115 Sister Chromatid Exchange: A Rapid Quantitative Measure of Genetic Injury.** (Eng) Carrano, A. V. (No affiliation given). *Energy Technol Rev* 1-8; 1978.

The phenomenon of sister chromatid exchange (SCE) is proposed as a means of rapidly screening potentially carcinogenic and mutagenic substances, establishing dose-response relationships, and assessing human exposure. SCE is known to increase when cells are exposed to carcinogens, but detection is now possible using bromodeoxyuridine (BrdUrd) incorporation into DNA for two cycles of replication; the distribution of BrdUrd-substituted DNA is the staining pattern with Hoechst dye 33258 or Giemsa stain, permitting the number of SCEs to be determined. When the rate of SCE was compared with the rate of mutation at the hypoxanthine phosphoribosyltransferase (hprt) locus after incubation of Chinese hamster cells with the mutagens ethyl methanesulfonate (EMS), ethylnitrosourea (ENU), mitomycin C, or proflavine sulfate for 18 hr. All four chemicals yielded linear

dose-response curves for both SCE and the mutations, but the slopes differed for each carcinogen. The relative hierarchy of the SCE-mutation ratio was mitomycin C > proflavine sulfonate > EMS > ENU. Rabbits were injected ip each wk with mitomycin C, benzo(a)pyrene, or methylcholanthrene for 8 weeks, and their blood lymphocytes were cultured and analyzed for SCE. Small increases in SCE occurred that, after the fourth injection, did not return to normal within 1 wk but increased fourfold after the 5th wk and were sustained at this level for 5 wk. At that time SCE decreased to 2x the control level and remained there >4 mo. Human studies have indicated that persons (including children in utero) exposed to probable mutagens (eg, chemotherapeutic drugs and organic solvents) have elevated lymphocyte SCE levels. The SCE assay should provide the means to assess the extent and nature of the genetic burden induced in humans by environmental chemicals. (13 refs)

- 79-0116 The Mutagenicity of Methyl Orange and Metabolites Produced by Intestinal Anaerobes.** (Eng) Chung, K. T. (Food Sciences Inst., Purdue Univ., West Lafayette, IN, 47907); Fulk, G. E.; Andrews, A. W. *Mutat Res* 58(2/3): 375-379; 1978.

The azo dye methyl orange and the products of its conversion by anaerobic gut bacteria were tested for mutagenicity in the Ames *Salmonella typhimurium* assay using strains TA98, TA100, TA1535, TA1537, and TA1538, with and without S-9 rat liver microsome mix present. After incubation of methyl orange with the *Bacteroides fragilis* subspecies *thetaiotaomicron* and with a *Fusobacterium* species 2 for 17-19 hr, culture filtrates were analyzed by thin-layer chromatography (TLC) and 0.25 ml was incubated in the Salmonella assay. Culture filtrates from both species incubated with S-9 mix were mutagenic (as indicated by reversion to prototrophy) in strains TA1538 and TA98. Sulfanilic acid, N,N-dimethyl-p-phenylenediamine (DMPD), and an unknown impurity were isolated from the filtrates by TLC in addition to the methyl orange. The isolated impure DMPD, a commercial DMPD, and a laboratory-synthesized DMPD, as well as the unknown impurity were all found to be mutagenic when tested with strain 1538, whereas the sulfanilic acid was not. Impure isolated DMPD and synthesized DMPD demonstrated mutagenicity in a dose-dependent manner in strain TA1538 with S-9 mix, although a toxic effect was noted when concentrations >100 μg were used. It is suggested that these metabolic products could be reabsorbed from the digestive tract and act adversely on other body tissues to form tumors. (15 refs)

- 79-0117 The Induction of Dominant Lethal Mutations in *Tilapia mossambica* by Alkane Sulphonic Esters.** (Eng) Hemsworth, B. N. (Life Science Lab., Teesside Polytechnic, Cleveland, England); Wardhaugh, A. A. *Mutat Res* 58(2/3): 263-268; 1978.

A serial mating system was used to study the effects of methyl methanesulfonate (MMS) and dimethylmyleran on the tropical freshwater fish, *Tilapia mossambica*. Male fish were given MMS (50 or 70 mg/kg ip) before introduction of females to the aquarium. Those females observed eventually to be carrying eggs were replaced within 24 hr of mating. About 60 hr after mating, eggs and embryos were removed from the mother and developing embryos examined by a low-power microscope for 1 wk. There was a significant incidence in gross anatomical deformity in embryos conceived during the 3 wk following paternal treatment with 50 mg/kg MMS. At the higher dose, 50% of the relatively few embryos produced in the 1st wk were defective. In subsequent weeks, 30% of embryos were defective. Paternal MMS treatment also reduced the number of embryos actually produced compared with that in controls. The isomeric forms of dimethylmyleran were also embryopathic. The meso isomer (4 mg/kg) caused the deformation of 44% of embryos produced in wk 1; the same dose of the \pm isomer affected 62% of embryos. The drug-induced embryopathies appear to be due generally to defects manifest initially during gastrulation and to be comparable to the defective embryos produced in *Xenopus laevis* by sperm treatment with mutagens. (11 refs)

79-0118 Enhancement of Repair Replication in Mammalian Cells by Hydroxyurea. (Eng) Clarkson, J. M. (Science Park-Res. Div., Univ. Texas System Cancer Center, Smithville, TX, 78957). *Mutat Res* 52(2): 273-284; 1978.

The effect of hydroxyurea (HU) on DNA repair replication was studied in Chinese hamster ovary (CHO) cells. Mitotic cells were treated with UV light, methyl methanesulfonate (MMS), or nitrogen mustard and incubated in the presence of one of the four ^3H -labeled deoxyribonucleosides plus bromodeoxyuridine and fluorodeoxyuridine for 2 hr in the presence or absence of 2 mM HU. The amount of repair replication was quantitated on CsCl gradients. The uptake of each nucleoside was increased twofold by the presence of HU during the incubation period. Following MMS treatment, pool sizes for each of the nucleosides were estimated by varying the amount of exogenously supplied nucleoside. In each case, pool size was insensitive to HU. These data are consistent with reports that HU has a detrimental effect on DNA repair. HU does not appear to inhibit repair synthesis, but rather increases it so that ligation is prevented, with the result that excision and resynthesis continue in an uncontrolled manner. (24 refs)

79-0119 Postnatal and Transplacental Carcinogenic Effects of Methylmethanesulfonate (MMS) and Ethylmethanesulfonate (EMS) in Hooded Rats. (Ger) Schneider, J. (Institut für Allgemeine Pathologie und Pathologische Anatomie, Medizinische Akademie Erfurt,

Nordhauser Strasse 74, DDR-50 Erfurt, E. Germany); Warzok, R.; Schreiber, D.; Heiderstadt, R. *Exp Pathol (Jena)* 16(1-6): 157-167; 1978.

The postnatal and transplacental carcinogenic effect of methyl methanesulfonate (MMS) and ethyl methanesulfonate (EMS) was studied in inbred strain E hooded rats. Twenty-eight juvenile rats (Group 1) received 15 iv injections of MMS (first injection 100 mg/kg, remainder 50 mg/kg) at 2-wk intervals. Seven pregnant rats received 30 mg/kg MMS iv on the 21st day of pregnancy; the carcinogenic action was studied in 38 offspring (Group 2). Twenty-eight juvenile rats (Group 3) received 13-15 iv injections of EMS (110 mg/kg) at 2-wk intervals. Seven pregnant rats received 100 mg/kg EMS iv on the 21st day of pregnancy; 32 offspring were studied (Group 4). The animals were examined upon sacrifice or spontaneous death at 167-684 days. The numbers of tumor-bearing animals were 18/28 in Group 1 (25 tumors), 12/38 in Group 2 (13 tumors), 24/28 in Group 3 (51 tumors), and 5/32 in Group 4 (7 tumors). The incidence of tumors of the CNS and nerves was 18/25 in Group 1, 8/13 in Group 2, 46/51 in Group 3, and 4/7 in Group 4. The neural tumors were identified as astrocytomas, oligodendrogliomas, malignant neurinomas, and multicentric sarcomas; the extraneural tumors comprised sarcomas, carcinomas, malignant lymphomas, stem-cell leukemia, and chronic myelosis. Three neurogenic tumors and one case of chronic myelosis were found in 4/14 mothers in Groups 2 + 4. The findings indicate the marked neurotropic action of MMS and EMS following postnatal and transplacental exposure. (39 refs)

79-0120 Induction of Purine Analog-resistant Mutants in Adult Rat Liver Epithelial Lines by Metabolic Activation-dependent and -Independent Carcinogens. (Eng) Tong, C. (Naylor Dana Inst. Disease Prevention, American Health Foundation, 1 Dana Road, Valhalla, NY, 10595); Williams, G. M. *Mutat Res* 58(2/3): 339-352; 1978.

In adult rat liver epithelial cultures, 6-thioguanine was superior to 8-azaguanine in the selection of purine analog-resistant mutants. The incidence of purine analog-resistant mutants increased as a result of exposure to a metabolic activation-dependent carcinogen [methyl methanesulfonate (MMS)] or to activation-independent carcinogens (aflatoxin B1, dimethyl sulfoxide, N-2-fluorenylacetamide). Expression time studies revealed that an interval of about 10 days between carcinogen exposure and mutant selection was required to recover the max number of mutants. The parental cell type and its mutants were comparable in sensitivity to the toxic effects of MMS. These data on increasing mutant incidence with time following exposure and the lack of specific resistance of the mutants to toxic effects of mutagenic carcinogens indicate that increased mutant incidence was due to mutant induction rather than to selection. Thus, rat liver epithelial cell cultures provide a self-sufficient screening system for carcinogens/mutagens. (54 refs)

79-0121 Detection of Alkylating Agents by the Analysis of Amino Acid Residues in Hemoglobin and Urine. 1. The In Vivo and In Vitro Effects of Ethyl Methanesulfonate, Methyl Methanesulfonate, Hycanthone Methanesulfonate, and Naltrexone. (Eng) Truong, L. (Preventive Medicine and Community Health, Div. Environmental Toxicology and Epidemiology, Univ. Texas Medical Branch, Galveston, TX, 77550); Ward, J. B.; Legator, M. S. *Mutat Res* 54(3): 271-281; 1978.

The effect of three alkylating agents, ethyl methanesulfonate (EMS), methyl methanesulfonate (MMS), and hycanthone methanesulfonate (HMS), and the narcotic antagonist naltrexone on the amino acid compositions of rat and human Hb was examined. Because the amino acid compositions of these proteins are well-established, changes in the molar ratios of specific amino acids could be monitored in purified Hb samples. Ratios of histidine, which is readily attacked by alkylating agents, to proline, which is not, were consistent in Hb purified from untreated blood samples from 14 male albino Sprague-Dawley rats and 25 human subjects. Treatment of Hb in vitro or in vivo with MMS, EMS, or HMS resulted in a loss of histidine residues relative to proline or phenylalanine. The decrease in histidine content increased with treatment dose and time and reached a max at about 15% of total histidine. Treatment of rats with MMS resulted in an increased urinary excretion of methylhistidines. Naltrexone had no direct effect on Hb in vitro, but it increased the proportion of methylhistidines in the urine of treated animals. (14 refs)

79-0122 Effect of 1,2-Dibromoethane (DBE) on Meiotic Chromosomes of *Tradescantia*. (Eng) Ma, T. H. (Dept. Biology, Brookhaven Natl. Lab., Upton, NY, 11973); Sparrow, A. H.; Schairer, L. A.; Nauman, A. F. *Mutat Res* 58(2/3): 251-258; 1978.

The production of micronuclei (MCN) in tetrads of microsporogenesis of *Tradescantia* clone 4430 (*T. hirsutiflora* x *T. subcaulis*) by a 6-hr treatment with 1,2-dibromoethane (DBE) gas showed a positive correlation with the concentration of DBE administered. A range of 0.001-0.002 MCN/tetrad/ppm hr was established by dose-effect experiments. The dose-response curve of the present study resembled that of a previous study on pink mutation in stamen hairs of the same clone of plants. A comparison of MCN/tetrad and pink mutation/stamen hair showed that the mutagenic efficiency of DBE in MCN induction is approx 36 times that of its efficiency in pink mutation induction. This is due to the fact that each of the 12 chromosomes of the meiocyte has many sites for chromosome or chromatid aberrations resulting in MCN, whereas only 1 site in 12 chromosomes of each stamen hair cell will permit expression of a pink mutation. (18 refs)

79-0123 Epoxide-Nucleophile Interactions: Acid-catalyzed Reaction of Ethylene Oxide with Water.

(Eng) Politzer, P. (Dept. Chemistry, Univ. New Orleans, New Orleans, LA, 70122); Daiker, K. C.; Estes, V. M.; Baughman, M. *Int J Quant Chem Quant Biol Symp* (5): 291-299; 1978.

The acid-catalyzed ring-opening interaction of ethylene oxide with water was studied. The effect of protonation in facilitating the opening of the epoxide ring involved at least two factors: a lengthening, and presumably weakening, of the C-O bonds and a change in the calculated atomic charges on the carbons from negative to positive, which should make them more reactive toward nucleophiles. A cis mode of attack by the water molecule was energetically favored over a trans mode. Several structures indicated that the key role may be played by internal hydrogen bonding. (20 refs)

79-0124 Structural Correlations of Carcinogenic and Mutagenic Alkyl Halides. (Eng) Simmon, V. F. (SRI International, Menlo Park, CA, 94025). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977*. Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 163-171; 1978.

The Ames *Salmonella typhimurium* microsome assay, using strain TA100, was used to determine the mutagenicity of 23 alkyl halides, 10 of which were unknown carcinogens. Twenty-one of these halides were mutagenic with and without S-9 liver microsome mix. The mutagenic compounds (c denotes proven carcinogen) included methyl bromide, methyl chloride, methyl iodide (c), methylene chloride (c), bromochloromethane, methylene bromide, bromoform (c), dibromochloromethane, bromodichloromethane, vinyl chloride (c), vinylidene chloride (c), 1,1,2-trichloroethylene (c), bis(2-chloroethyl) ether (c), bis(2-chloroisopropyl) ether, 1-chloropropene, 3-chloropropene, epichlorohydrin (c), hexachlorobutadiene, 3-bromopropionic acid, 3-iodopropionic acid, and 3-chloropropionic acid. Two known carcinogens, carbon tetrachloride and chloroform, were not mutagenic in the presence or absence of the S-9 mix. It is likely that an insufficient amount of the mutagenic form was produced or that this form was so unstable it was unavailable to interact with the bacterial DNA. In general, the mutagenicity correlated with chemical reactivity. Of interest was the mutagenicity of methylene chloride, a widely used industrial chemical with broad environmental exposure (via paint removers and aerosol spray cans). (17 refs)

79-0125 Studies on the Mutagenicity of Vinyl Chloride Metabolites and Related Chemicals. (Eng) Laumbach, A. D. (Dept. Microbiology and Immunology, Univ. Louisville Sch. Medicine, Louisville, KY, 40201); Lee, S.; Wong, J.; Streips, U. N. In: *Third International Symposium on the Detection and Prevention of Cancer held by the*

International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 155-170; 1977.

The mutagenicity and potential mechanisms of action of several vinyl chloride (VC) metabolites [chloroacetaldehyde (CAA) monomer hydrate, CAA dimer hydrate, and CAA trimer] and epichlorohydrin (ECH, a carcinogenic chlorooxirane homolog) were studied. Indirect mutagenicity assays using repair-deficient *Bacillus subtilis* strains and direct mutagenicity assays using *Salmonella typhimurium* were performed. The mutagenicity of CAA and chlorooxirane was confirmed and that of the VC metabolites and ECH was found. Neither acetaldehyde, chloroacetic acid, nor chloroethanol showed a significant level of mutagenicity. There may be a molecular relationship involving the proximity of the chloride group to the aldehyde moiety for mutagenicity. Recombination repair appeared to be the mechanism for correcting VC metabolite-elicited damage. CAA decreased the biological activity of transforming DNA only if the cells were treated with the mutagen prior to DNA extraction. In vitro studies showed no such effect. The mode of action of ECH differed from that of the VC monomer metabolites. Although it caused similar base-substitution mutations in *Salmonella* strain TA100, it was a comparatively weaker alkylating agent. ECH also exhibited a lower toxicity level than VC monomer metabolites and thus demonstrated mutagenicity through a wider range of concentrations. ECH produced higher levels of mutation in *Salmonella* cultures that were actively replicating DNA than in cultures that were arrested in DNA replication. (29 refs)

79-0126 Mutagenicity of Aliphatic Epoxides. (Eng) Wade, D. R. (Coll. Pharmacy, Univ. Michigan, Ann Arbor, MI, 48109); Airy, S. C.; Sinsheimer, J. E. *Mutat Res* 58(2/3): 217-223; 1978.

The mutagenicity of 17 aliphatic epoxides was determined using the *Salmonella typhimurium* mutants developed by Ames. In strains TA100 and TA1535, the activity of these epoxides and those reported in the literature, depended on the degree of substitution around the oxirane ring. Monosubstituted oxiranes were the most potent mutagens in both strains. 1,1-Disubstitution resulted in the complete loss or reduction of mutagenicity. *trans*-1,2-Disubstituted and tetrasubstituted oxiranes were not mutagenic, and the *cis*-1,2-disubstituted oxiranes tested were weakly mutagenic in strain TA100 only. For the monosubstituted compounds, the presence of electron-withdrawing substituents increased mutagenicity. (17 refs)

79-0127 The Effect of Chronic Ethanol Intake on the Growth and Spread of Some Murine Tumors. (Eng) Capel, I. D. (Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey RH8 0TL, England); Jen-

ner, M.; Pinnock, M. H.; Dorrell, H. M.; Williams, D. C. *Oncology* 35(5): 224-226; 1978.

The effect of ethanol on the growth and spread of B16 melanoma, Ehrlich ascites cells, and Lewis lung carcinoma was investigated in C57BL/6 and Theiller-Original mice. The mice were divided into three groups for ethanol treatment: (1) pretreated, given a 10% ethanol soln in place of drinking water for 2 wk prior to inoculation of tumor cells; (2) post-treated, given the ethanol soln after injection of tumor cells; and (3) control, injected with tumor cells but given no ethanol. Animals from each group were inoculated im with 4.6×10^6 B16 melanoma cells, ip with 3.5×10^6 Ehrlich ascites cells, or im with 2×10^6 Lewis lung carcinoma cells. There was no significant difference between the pre- and posttreated animals. The treatment had no effect on the B16 melanoma, but the number of Ehrlich ascites cells were reduced by ethanol ingestion. In the case of the Lewis lung carcinoma, administration of ethanol for 2 wk tended to lower the number of metastases to the lung without significantly affecting the primary tumor size; more prolonged ethanol intake (up to 8 wk) decreased both the wt of the primary tumor and the rate of metastasis to the lung. The inhibitory effect of ethanol on metastasis and primary tumor growth could be due to an effect on the metabolism of the host and/or the tumor. The replication of the tumor cells may have been limited by an ethanol-induced decrease in nutrients or energy availability. These results do not corroborate reported correlations between alcohol intake and increased tumor incidence in humans. (18 refs)

79-0128 The Effect of Chloroform Ingestion on the Growth of Some Murine Tumours. (Eng) Capel, I. D. (Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey RH8 0TL, England); Williams, D. C. *IRCS Med Sci (Cancer)* 6(10): 435; 1978.

Administration of chloroform (in drinking water) to male T0 mice did not enhance the growth or metastasis of Lewis lung carcinoma (LLC) or significantly increase the number of Ehrlich ascites tumor (EAT) cells at a level of 0.15 mg/kg/day. At 15 mg/kg/day, there was a significant increase in LLC foci and in the number of EAT cells. The percentage of organs invaded by B16 melanoma cells was greater in animals treated with either dose level than in controls. (4 refs)

79-0129 Immunopathologic Observations in Liver Angiosarcoma. (Eng) Espinosa, E. (Dept. Pathology, Univ. Louisville Sch. Medicine, Louisville, KY). In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 927-939; 1977.*

To develop a more sensitive liver function test for the early detection of vinyl chloride liver disease, an attempt was made to discover antigenic changes in angiosarcomatous tissue and to test for the presence of an antibody response in the host. Serum, liver, and adjacent tissue samples were obtained at autopsy from 2 individuals with vinyl chloride-associated angiosarcoma and 10 control individuals with normal liver function and at biopsy from 10 patients with liver dysfunction with fibrosis. Immunodiffusion studies of angiosarcomatous tissue revealed the presence of an antigen not found in normal liver or kidney, but found in normal lung and spleen. This protein was inactivated by Pronase and trypsin, was heat- and acid pH-labile, and was found to precipitate at concentrations of 20-30% saturated ammonium sulfate and 30-70% ethanol. Immunoelectrophoretic assays of angiosarcomatous tumor extracts revealed the absence of one normal tissue antigen characterized as an entity unaffected by Pronase, trypsin, and heat treatment, inactivated by periodate and acid pH, and which precipitated over a wide range of conditions. Additionally, immunofluorescence assays of angiosarcomatous tissue indicated the presence of bound IgG. Further studies are necessary to determine whether this tumor-bound IgG represents specific antitumor antibody or antibody fixed by the tumor tissue nonspecifically. (29 refs)

79-0130 Urinary and Tissue Glycosaminoglycan Patterns in Hepatic Angiosarcoma. (Eng) Kupchella, C. E. (Cancer Center, Dept. Medicine, Univ. Louisville Sch. Medicine, Louisville, KY, 40201); Tamburro, C. H. In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 915-926; 1977.

To evaluate the use of glycosaminoglycan (GAG) patterns as an early indicator of vinyl chloride (VC)-induced liver injury or angiosarcoma (AS), GAG patterns were determined in urine samples of 9 patients with histories of exposure to VC and who had abnormal liver biochemistry, 6 with "other" cancers prior to surgery, 3 with AS, 8 with viral hepatitis, 6 with cirrhosis, 2 with lung-liver metastases, and 4 with metabolic liver disorders. Determinations of GAG were carried out by creatinine and uronic acid assays. Additionally, tissue samples taken at autopsy from 2 patients with AS, 2 with cirrhosis, and 3 controls (who had gun-shot wounds) were similarly analyzed. Results showed that AS, hepatitis, cirrhosis, and liver metastases all involved elevated GAG excretion. Tissue data indicate that these elevated levels reflect GAG elevation in the liver. Furthermore, results disclosed that the chondroitin sulfates are the primary urinary GAG in both normal controls and in patients, while chondroitin sulfates and heparin are the dominant GAG present in fibrotic, nontumor portions of AS livers and tumor tissue, respectively. It is concluded that the increases in liver and urinary GAG levels may well reflect an important role of

these substances in the process of fibrogenesis and tumor growth. (31 refs)

79-0131 Electronic Properties of Protein--Methylglyoxal Complexes: Strong Evidence for Energy-Band Conduction. (Eng) Pethig, R. (Lab. Natl. Foundation Cancer Res., Univ. Coll. North Wales, Dean St., Bangor, Gwynedd LL57 1UT, Wales). *Int J Quant Chem Quant Biol Symp* (5): 159-171; 1978.

Further studies were made of the dielectric and electronic properties of various protein-methylglyoxal (MG) complexes. Piezoelectric properties, microwave Hall effect, hydration isotherm properties, steady-state conduction, and dielectric properties were measured over the effective frequency range 10^{-5} to 10^{10} hertz. The extent of the binding of MG was established using ^{14}C -labeled MG and scintillation counting. The interaction of MG with proteins resulted in a brown complex that exhibited increased electronic activity compared with normal untreated proteins. This complex had an increased free-electron spin density, steady-state conductivity, and piezoelectric response. Unlike the untreated proteins, the protein complexes also exhibited a distinct low-frequency dielectric dispersion, and at 10 gigahertz there was a reversal of the usual electric-field saturation of polarizability. Compared with normal casein, the casein complex exhibited an increase in monolayer hydration capacity. These effects suggest that when MG is incorporated into the structure of a protein molecule, a charge-transfer interaction occurs, resulting in the creation of mobile electron "holes." This satisfies the basic prerequisite for the applicability of Szent-Gyorgyi's electronic theory of the "living state" and of cancer. (30 refs)

79-0132 Plasmacytomas of the NZB Mouse. (Eng) Morse, H. C. (Lab. Microbial Immunity, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20014); Riblet, R.; Asofsky, R.; Weigert, M. *J Immunol* 121(5): 1969-1972; 1978.

Myeloma proteins derived from distinct genetic pools were compared for sequence specificity differences or similarities following plasmacytoma induction in > 10,000 NZB mice (6-8 wk of age) that were injected ip with 0.05 ml pristane (2,6,10,14-tetramethylpentadecane) at three bimonthly intervals. Approx 50% of the total number of tumors were induced by 1 yr, and the rest developed before 20 mo, but this induction period was longer than that previously observed for BALB/c mice. Of these tumors, 77% were diagnosed as plasmacytomas. Samples of tumor ascites fluids were analyzed for paraproteins by immunoelectrophoresis with specific antisera and the results compared with a previously reported series of BALB/c mice plasmacytomas; 82% of NZB ascites contained a detectable paraprotein (similar to the BALB/c series), but fewer NZB ascites contained IgA (20.3% versus

45.5%) and more contained IgG (41.7% versus 19.7%) than in the BALB/c series. Furthermore, 8.2% of NZB ascites contained paraproteins that could not be assigned to a particular heavy chain class, whereas all ascites were classifiable in the BALB/c series. Only 4/595 paraprotein-containing NZB ascites bound any carbohydrate antigen tested, 10x less than in the BALB/c series. Although 56 NZB tumors produced ascites with more than one paraprotein, 0/25 were shown to produce more than one following serial transplantation, indicating that these polysecreting tumors probably reflected the independent occurrence of two separate malignant clones. The observed differences between the two series suggest that the cell populations susceptible to malignant transformation may be different in BALB/c and NZB mice. (13 refs)

79-0133 Combined Cytogenetic Effects of Endosulfan & Metepa in Male Rats. (Eng) Dikshith, T. S. (Industrial Toxicology Res. Centre, Lucknow 266 001, India); Nath, G.; Datta, K. K. *Indian J Exp Biol* 16(9): 1000-1002; 1978.

The combined effects of endosulfan (ES, a widely used insecticide and acaricide) and metepa (MT, a sterilizing agent against insect vectors) on the chromosomes of male albino rats were studied. The rats were given ES (11.6 mg/kg/day) and/or MT (13.6 mg/kg/day) po for 30 days. Cytogenetic assays of bone marrow and spermatogonial cells showed that ES did not cause any significant chromosomal aberrations in the rats. However, MT alone and in combination with ES increased the number of aberrant cells and chromatid breaks in spermatogonial and bone marrow cells, particularly in the latter. These increases were greater with MT alone. The mitotic index in control, ES-, ES- + MT-, and MT-treated cells was 56%, 26.6%, 19.13%, and 22.29%, respectively, in the bone marrow cells and 28%, 21%, 11.08%, and 14.16% in the spermatogonial cells. The results show that MT produces significant cytogenetic changes in the rat and that ES and MT do not potentiate each other. (19 refs)

79-0134 Cytotoxic Effects of Toximul MP8 in Human Lymphocytes in Culture: A Preliminary Investigation. (Eng) Petropolis, P. N. (Lab. Radiation Biology, Dalhousie Univ., Halifax, Nova Scotia, Canada); Kamra, O. P. *Mutat Res* 58(2/3): 287-291; 1978.

The cytotoxic effects of Toximul MP8 a commercial emulsifier formulation used as an insecticide carrier, on human lymphocytes were assessed by measuring mitotic index, DNA labeling index, and the frequency of chromatid breaks. The Toximul MP8 was added in amounts of 10, 20, 30, or 40 ppm together with phytohemagglutinin to human whole blood, which was cultured for 52 hr. The mitotic index decreased from 10.44% at 0 ppm to 0.24% at 40 ppm. The percent of lymphocytes incorporating (³H)thymidine from 32-35 hr of

culture also decreased with an increase in the Toximul MP8 concentration. The labeling index of 17.38% in control cultures dropped to 5.62% and 0.39% at 20 and 40 ppm, respectively. A significantly increased percentage of abnormal metaphases was observed even at the 10 ppm Toximul MP8 concentration. Based on these preliminary studies, the continued use of Toximul MP8 as an insecticide carrier-emulsifier in an aerial spray program in populated areas should be questioned. (12 refs)

79-0135 Mutagenic Action of Aromatic Epoxy Resins. (Eng) Andersen, M. (Dept. Microbiology, Royal Danish Sch. Pharmacy, 2 Universitetsparken, DK-2100 Copenhagen O, Denmark); Kiel, P.; Larsen, H.; Maxild, J. *Nature* 276(5686): 391-392; 1978.

Three aromatic epoxy resins, Epikote 828 (E828), Epikote 1001 (E1001), and Epikote 1004 (E1004) were tested for mutagenicity by comparison with the positive control substance epichlorhydrin (ECH; a simple epoxide) in the plate incorporation assay with histidine-requiring mutants of *Salmonella typhimurium*. E828, the most active resin tested, and E1001 were both more mutagenic than was ECH in tester strain TA100. Although the mutagenicity of ECH was similar in both tester strains TA100 and TA1535, that of the resins was much lower in TA1535 than in TA100, showing that residual ECH in the resins was not the sole cause of the resins' actions. When rat liver microsomes containing NADP were added to the culture plates, the activities of both the resins and of ECH decreased 10-fold in strain TA100; whereas in strain TA1535, E828 was activated in the presence of NADP, and inactivated in its absence. E1001 showed a similar tendency in relation to NADP. The activity of ECH was reduced almost 10-fold in TA1535 assay with microsomes, independent of the presence of NADP. The activation of the epoxy resins seen in TA1535 was not caused by decomposition of the compounds and liberation of constituent bisphenol A (2,2-bis(4-hydroxyphenyl)propane), because this compound was not mutagenic in either tester strain with or without added liver microsomes when tested separately. The results demonstrate a potential cancer risk in man from the three resins tested. (16 refs)

79-0136 Mutagenic Action of Some Hair Dyes Manufactured in Czechoslovakia. (Cze) Havova, R. (Lekarska Fakulta, UJEP, Brno, Czechoslovakia); Soskova, L.; Hava, P. *Cesk Hyg* 23(9): 383-388; 1978.

Twenty-five Czechoslovakian Regonol hair dye preparations were tested for antigenicity in the Ames test, using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538. The Regonol preparations contain p-phenylenediamine, resorcinol, p-aminophenol, p-nitro-o-aminophenol, o-nitro-p-phenylenediamine and picramic acid. Seven preparations showed marked mutagenic

activity. Twenty preparations were tested with TA 98 with activation by mouse liver microsomal fraction. Thirteen preparations were found to be mutagenic, and two others suspect as mutagenic in this test. All mutagenically active preparations reacted with the detector strains TA 98 and TA 1538, which detect mutations in guanidine and cytosine sequences. The findings suggest that these dyes are potentially dangerous for their users, and especially for hairdressers and persons engaged in their manufacture. (22 refs)

- 79-0137 Half-wave Potentials and LCAO-SCF-MO Calculations for Carcinogenic Benz(c)acridines.** (Eng) Okano, T. (Pharmaceutical Inst., Tohoku Univ., Tohoku, Japan); Haga, M.; Ujii, K.; Motohashi, N. *Chem Pharm Bull (Tokyo)* 26(9): 2855-2859; 1978.

The half-wave reduction potential and half-peak oxidation potential were measured for 11 methyl-substituted benz(c)acridines and unsubstituted benz(c)acridine in acetonitrile with tetraethylammonium perchlorate electrolyte. A linear correlation was obtained between the energy of the lowest unoccupied molecular orbital as calculated by the LCAO-SCF method and the half-wave reduction potential. A correlation also existed between the energy of the highest occupied molecular orbital and the half-peak oxidation potential. The carcinogenic activities of the derivatives were highly correlated with the electron density, the electrophilic superdelocalizability of the K-region, the electron density for the ring nitrogen atom of the compound, and the reactivity index. The data suggest that the electrophilic reactivity of the K-region or the ring nitrogen atom is almost essential for the carcinogenic activity of the methyl-substituted benz(c)acridines. (16 refs)

- 79-0138 Carcinogenic Benzo(a)pyrene Metabolites Bound to DNA: Metabolic Formation by Human Cultured Lymphocytes and by Human Liver Microsomes.** (Eng) Boobis, A. R. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20014); Atlas, S. A.; Nebert, D. W. *Pharmacology* 17(5): 241-248; 1978.

The formation of carcinogenic benzo(a)pyrene (BP) metabolites that bind to DNA by cultured human lymphocytes and human liver microsomes was investigated. Cultured human lymphocytes were activated by incubation with pokeweed mitogen plus phytohemagglutinin M prior to treatment with 3-methylcholanthrene (MC). Sonicates of these cells were incubated with deproteinized DNA (20 mg), (³H)BP (60 nmol), and an NADPH-generating system. With both control and MC-treated lymphocytes, two BP metabolite-nucleoside chromatographic peaks were detected. The major peak represented the 4,5-oxide bound to nucleoside(s) and the lesser

represented quinone-oxide(s). There was no correlation between the aryl hydrocarbon hydroxylase activity (or its inducibility) and the BP metabolites generated by the lymphocytes and bound to DNA in vitro, due perhaps to limiting amounts of epoxide hydase in cultured human lymphocytes; it is further suggested that, in tissues such as lung, which have very low epoxide hydase activity, intermediates such as those generated by further metabolism of quinones or the 4,5-oxide may represent the ultimate carcinogenic forms. At least six BP metabolite-nucleoside chromatographic peaks were identified when human liver microsomes were examined. The major peak represented the 7,8-diol-9,10-epoxides bound to nucleoside, which is believed to be one of the ultimate carcinogenic forms of BP. It is suggested that it might be possible, by assaying liver or other tissue from a number of subjects, to determine if there are inter-individual differences in the capacity to produce this metabolite. (42 refs)

- 79-0139 Potentiation of Steroid Binding to Proteins by 7,12-Dimethylbenz(a)anthracene.** (Eng) Barlow, J. W. (Downie Metabolic Unit, Alfred Hosp., Prahran, Victoria, Australia, 2010); Minasian, L. C.; Funder, J. W. *J Steroid Biochem* 9(11): 1027-1032; 1978.

The possibility that the carcinogenic action of 7,12-dimethylbenz(a)anthracene (DMBA) may occur through an interaction with target tissue receptors for steroid hormones was studied. Cytosols were prepared from uterus and mammary gland of 45-day-old adrenalectomized and ovariectomized rats that had been either untreated or primed with estradiol benzoate (0.4 mg/100 g/day sc for 3 days prior to sacrifice). The cytosols were incubated for 90 min with various steroids with and without DMBA (10^{-6} M). DMBA did not affect the binding of (³H)-estradiol or of (³H)-dexamethasone but increased the binding of (³H)-progesterone [(³H)-P; 10^{-8} M]. The enhanced binding of (³H)-P in the presence of DMBA was specific, since it was displaceable by excess unlabeled P. Potentiation of (³H)-P binding was not confined to potential P target tissues; DMBA also potentiated binding of ³H-P to bovine serum albumin, ovalbumin, catalase, and rat plasma. Over the range of protein and DMBA concentrations studied, potentiation of (³H)-P binding increased with increasing DMBA concentrations (1-30 μ M) and decreased with increasing protein concentrations (0.003-0.1 mg/ml). Potentiation appeared restricted to a protein concentration < 1 mg/ml. Among a number of steroids studied, the hierarchy of DMBA-potentiated binding was (³H)-P > (³H)-R 5020 (17,21-dimethyl-19-nor-4,9-pregnadiene-3,20-dione) > (³H)-deoxycorticosterone. 3-Methylcholanthrene, a less potent carcinogen than DMBA, had a similar but much less marked potentiating effect on steroid binding. A 10-fold increase in DMBA concentration resulted in a 100-fold increase in bound (³H)-P, indicating a cooperative phenomenon. These results suggest that DMBA may be active at a precellular level via modification of the effector actions of progesterone. (15 refs)

79-0140 Cytogenetic Toxicity of Gentian Violet and Crystal Violet on Mammalian Cells In Vitro.

(Eng) Au, W. (Dept. Biology, Univ. Texas System Cancer Center, M. D. Anderson Hosp., Tumor Inst., Houston, TX, 77030); Pathak, S.; Collie, C. J.; Hsu, T. C. *Mutat Res* 58(2/3): 269-276; 1978.

The cytogenetic toxicity of gentian violet (a triphenylmethane dye) and its related compound, crystal violet, were tested in various mammalian cells in vitro. Chinese hamster ovary (CHO) cells treated for 8 hr with a 10 µg/ml gentian violet showed a significant accumulation of abnormal metaphases as evidenced by their elevated mitotic index and metaphase/anaphase ratio. The chromosome aberrations induced by gentian violet were both dose- and duration-dependent. At 0.5 and 5.0 µg/ml, gentian violet also induced chromosome aberrations in human lymphocyte cultures, HeLa cells, L cells, and in fibroblast lines derived from *Peromyscus eremicus* and from the Indian muntjac. At 5 µg/ml gentian violet, the *Peromyscus* cells exhibited complete mitotic inhibition. In a comparative study of the effect of 11 triphenylmethane dyes (various gentian and crystal violets) on the chromosomes of CHO cells, most dye samples induced severe damage to chromosomes. These results indicate that both gentian violet and crystal violet are clastogenic and should be regarded as biohazardous substances. (16 refs)

79-0141 Clinical and Pathological Effects of Cigarette Smoke Exposure in Beagle Dogs. (Eng) Zwick-

er, G. M. (Stauffer Chemical Co., Farmington, CT); Filipy, R. E.; Park, J. F.; Loscutoff, S. M.; Ragan, H. A.; Stevens, D. L. *Arch Pathol Lab Med* 102(12): 623-628; 1978.

The clinical and pathological effects of high (4.6 mg) nicotine (HN) and low (1.4 mg) nicotine (LN) cigarette smoke administered via tracheostomy to young adult male beagle dogs in doses of 6 or 12 cigarettes/day were determined. The dogs were exposed 7 days/wk for 5 mo. Tracheobronchitis was common in dogs given 12 HN cigarettes/day, with accompanying recurrent fever and thick discharge from the tracheal stroma. In dogs given 12 cigarettes/day, leukocytosis was consistently noted in both HN- and LN-treated animals throughout the exposure period. At necropsy, the left diaphragmatic lobe of the lungs was significantly heavier in dogs exposed to 12 cigarettes/day; the right apical lobe was significantly heavier in all the smoke-exposed dogs. Lesions were confined primarily to the lungs and tracheobronchial lymph nodes, which were approx 2X normal size and discolored brownish-black. Histopathologically, there were basal cell hyperplasia of the larynx, trachea, bronchial tree, and respiratory mucosa; alveolitis and alveolar type 2 epithelial cell hyperplasia; alveolar histiocytosis; "smoke granulomas"; and fibrosis in virtually all smoke-exposed animals. Dogs on 12 cigarettes/day-regimens usually also had accompanying squamous metaplasias, and in these animals there were three cases of suppurative bronchopneumonia (all were HN trea-

ted). Rhinitis, turbinate basal epithelial cell hyperplasia, and squamous metaplasia were increased in dogs in the HN versus those in the LN cigarette group. Alveolar emphysema was infrequently found, but it is suggested that this was due to the relatively short duration of the experiment. (25 refs)

79-0142 Formation and Determination of Ethyl Carbamate in Tobacco and Tobacco Smoke. (Eng)

Schmeltz, I. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595); Chiong, K. G.; Hoffmann, D. *J Anal Toxicol* 2(6): 265-268; 1978.

The formation of ethyl carbamate (EC, urethan) from maleic hydrazide (MH) was investigated in model studies, and a method for determining EC in tobacco products was developed. The method includes solvent partition, column chromatography, and gas chromatography/mass spectrometry. The smoke of MH-treated and untreated tobaccos contained comparable amounts of EC (20-38 nanograms/cigarette), as did treated and untreated tobaccos (310 and 375 nanograms/g, respectively). (13 refs)

79-0143 Exposure of Nonsmokers to the Gaseous and Particulate Phases of Cigarette Smoke. (Dan)

Hugod, C. (Klinisk-kemisk afdeling CL, Rigshospitalet, DK-2100 Copenhagen O, Denmark); Hawkins, L.; Astrup, P. *Ugeskr Laeg* 140(44): 2707-2711; 1978.

The effects of exposing volunteers to different components of sidestream cigarette smoke in an unventilated room were determined. The concentrations of both the gaseous and particulate components of the cigarette smoke decreased, probably due to inhalation and adsorption on the skin, hair, and clothing of the volunteers. However, it is emphasized that when healthy nonsmokers are exposed to tobacco smoke under realistic circumstances, they are not exposed to levels that would produce a permanent health hazard. (25 refs)

79-0144 Characterization of Catechols, Resorcinols, and Hydroquinones in an Acidic Fraction of Cigarette Smoke Condensate. (Eng) Schlotzhauer, W. S. (Natl.

Inst. Environmental Health Service, Research Triangle Park, NC, 27709); Walters, D. B.; Snook, M. E.; Higman, H. C. *J Agric Food Chem* 26(6): 1277-1281; 1978.

Gel filtration chromatography, gas chromatography-mass spectrometry, and UV spectroscopy showed that a biologically active subfraction of a weakly acidic fraction of cigarette smoke condensate contained catechol, resorcinol, and hydroquinone and their alkyl and methoxy derivatives plus 4-pyrone, vanillins, dimethoxyphenols, phenylphenols, and naphthols. (19 refs)

- 79-0145** High Pressure Liquid Chromatographic Determination of Patulin in Apple Juice. (Eng) Stray, H. (Food Inspection of Processed Fruits and Vegetables, Ministry Agriculture, Gladengyn, 3B, Oslo 6, Norway). *J Assoc Off Anal Chem* 61(6): 1359-1362; 1978.

The patulin (PL) content of 140 apple juice samples was analyzed. PL was extracted from apple juice with ethyl acetate, the extract was purified by elution from a silica gel column with ethyl acetate-toluene, and the eluate was subjected to high-pressure liquid chromatography. The samples contained $< 1\text{-}220\text{ }\mu\text{g/liter}$ PL. The lower detection limit was $1\text{ }\mu\text{g/liter}$; the mean recovery of added PL was 82.6%. (5 refs)

- 79-0146** Differential Expression of Oncogenicity and Nopaline Synthesis in Intact Leaves Derived from Crown Gall Teratomas of Tobacco. (Eng) Wood, H. N. (Lab. Plant Biology, Rockefeller Univ., New York, NY, 10021); Binns, A. N.; Braun, A. C. *Differentiation* 11(3): 175-180; 1978.

The expression of oncogenicity and nopaline synthesis in crown gall teratoma tissues of tobacco was studied. The expansion phase of teratoma-derived leaf tissue fragments planted on a basic culture medium could be reproduced in normal leaf tissues when fragments of the latter were isolated and planted on basic culture medium supplemented with an auxin (naphthaleneacetic acid, 0.25 mg/liter). Thus, auxin was persistently synthesized in the isolated teratoma-derived fragments. An active, de novo synthesis of nopaline from arginine occurred in the essentially resting cells present in intact teratoma-derived leaves, but it did not appear to occur in intact normal tobacco leaves of comparable age and stage of development. The data indicate that while an active and persistent de novo synthesis of nopaline occurs in intact teratoma-derived leaves, a reexpression of oncogenicity depends on the development of new cell divisions. These new cell divisions may be required to reestablish positive feedback control mechanisms upon which the development of a capacity for autonomous tumor tissue growth depends or to establish the pattern of metabolism concerned with cell growth and division that is then maintained in the plant tumor cells by positive feedback control mechanisms. (8 refs)

- 79-0147** Effect of Agrocin 84 on Attachment of *Agrobacterium tumefaciens* to Cultured Tobacco Cells. (Eng) Smith, V. A. (Dept. Biochemistry, Univ. Bristol Medical Sch., University Walk, Bristol, England); Hindley, J. *Nature* 276(5687): 498-500; 1978.

Initial stages in the transformation of cultured tobacco cells to crown gall tumor cells by *Agrobacterium tumefaciens* C58 were investigated, along with the role of agrocin 84 (A84), an intraspecific antibiotic produced by the nonpathogenic

strain *A. tumefaciens* K84, in preventing tumorigenesis. Tobacco cell cultures and wounded tobacco plants were inoculated with aliquots of untreated and A84-treated suspensions of strain C58 (which harbors the nopaline-type tumorigenic plasmids) and its avirulent, heat-cured derivative C58(NT-1). The cultures of C58 that induced tumor formation on wounded plants also induced nopaline synthesis in the cells, and both processes were blocked by A84. C58(NT-1) did not induce transformation. When C58 and C58(NT-1) were labeled with ^{32}P before A84 treatment and the experiments were repeated, it was found that $> 90\%$ of C58 remained associated with the tobacco cells after fractionation, vs only 15% of C58(NT-1). A84 reduced the affinity of C58 for its host by a factor of 2-3, but it did not significantly alter the binding capacity of C58(NT-1). Scanning electron microscopy of the infected tobacco cells demonstrated that the formation of a specific infection complex is essential for tumorigenesis. The envelopes of the A84-treated C58 cells, but not those of treated C58(NT-1) cells, were, when present, ill-defined and fragmented, and the cells contained large, electron-dense granules. Thus, A84 probably interferes with cell wall synthesis rather than acting on preformed structures; the granules may represent a build-up of cell wall precursors. The data suggest that the cell surfaces of C58 and C58(NT-1) are different and that this difference is due to the presence of the tumorigenic plasmid. A84 may prevent tumorigenesis by causing fragmentation or loss of the cell envelope, thereby impairing the ability of the bacterium to transfer tumorigenic DNA to its host. (28 refs)

- 79-0148** The Lack of Mutagenic Properties of Patulin and Patulin Adducts Formed with Cysteine in *Salmonella* Test Systems. (Eng) von Wright, A. (Technical Res. Center of Finland, Food Res. Lab., Biologinkuja 1, SF-02150, Espoo 15, Finland); Lindroth, S. *Mutat Res* 58(2/3): 211-215; 1978.

The fungal toxin patulin and patulin-cysteine adducts were tested for mutagenicity in an Ames'-type assay with *Salmonella typhimurium* strains TA100 and TA98, both in the presence and absence of a liver microsome preparation from male NMRI mice. Patulin in the amounts of 5, 10, 20, and $30\text{ }\mu\text{g}$ and patulin adducts of 900, 1,800, and 2,700 patulin-equivalent μg were tested. No mutagenicity was noted in any of the microsomal activation tests. A host-mediated assay was performed using *S. typhimurium* strains TA1950 and TA1951 in which gastric intubation of 20 and 10 mg/kg patulin or 2,800 and $1,400\text{ mg/kg}$ adduct mixture into NMRI mice was followed by injection of bacterial strains into the mouse peritoneum, incubation for 3 hr, retrieval of incubated peritoneal fluid, and plating of the bacteria. No differences were found in injected animals either internally or externally, and there were no differences in revertant frequencies or in viable counts of test bacteria. These results suggest that patulin reacts with some cell component to produce a secondary effect on the genetic apparatus of the cell that is not detectable in the *Salmonella* test system. (19 refs)

- 79-0149 Mutagenicity of Plant Flavonoids: Structural Requirements for Mutagenic Activity in *Salmonella typhimurium*.** (Eng) Macgregor, J. T. (Western Regional Res. Center, U.S. Dept. Agriculture, Berkeley, CA, 94710); Jurd, L. *Mutat Res* 54(3): 297-309; 1978.

Forty compounds that are structurally related to the plant flavonol quercetin were tested for mutagenic activity in *Salmonella typhimurium* strain TA98. Quercetin, myricetin, rhamnetin, galangin, kaempferol, tamarixetin, morin, 3'-O-methylquercetin, 7,4'-di-O-methylquercetin, and 5,7-di-O-methylquercetin exhibited unequivocal mutagenic activity. Quercetin, myricetin, rhamnetin, and 5,7-di-O-methylquercetin were active without metabolic activation, although it markedly enhanced their activity, whereas the other compounds required an in vitro rat-liver metabolizing system for significant activity. Quercetin and 2,3-dihydroquercetin exhibited weak mutagenic activity. Structural features that appear essential for mutagenic activity in TA98 are a basic flavanoid ring structure with these additional features: (1) a free hydroxyl group at the 3 position, (2) a double bond at the 2,3 position, (3) a keto group at the 4 position, and (4) a structure that permits the proton of the 3-hydroxyl group to tautomerize to a 3-keto compound. A B-ring structure that permits oxidation to quinoid intermediates appears to be a requirement. The same structural requirements appear to be necessary for mutagenicity in strain TA100. A metabolic pathway for flavonol activation to DNA-reactive species is proposed. (19 refs)

- 79-0150 Comparative Mutagenesis of Plant Flavonoids in Microbial Systems.** (Eng) Hardigree, A. A. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Epler, J. L. *Mutat Res* 58(2/3): 231-239; 1978.

The plant flavonoids quercetin (3,5,7,3',4'-pentahydroxyflavone), morin (3,5,7,2',4'-pentahydroxyflavone), kaempferol (3,5,7,4'-tetrahydroxyflavone), chrysin (5,7-dihydroxyflavone), fisetin (3,7,3',4'-tetrahydroxyflavone), myricetin (3,5,7,3',4',5'-hexahydroxyflavone), myricitrin (myricetin -3- rhamnoside), hesperetin (3',5,7-trihydroxy -4'-methoxyflavanone), quercitrin (quercetin-3-L-rhamnoside), rutin (quercetin-3-rhamnosylglucoside or quercetin-3-rutinoside), and hesperidine (hesperetin-7-rutinoside) were assayed for mutagenicity in the *Salmonella*/microsomal activation system. Quercetin, morin, kaempferol, fisetin, myricetin, quercitrin, and rutin were mutagenic with *Salmonella* strain TA98. Quercetin and myricetin were mutagenic without metabolic activation, although more effective when a rat liver microsomal preparation was included; the other flavonoids all required metabolic activation. The results with *Salmonella* were confirmed in strain D4 of *Saccharomyces* and in *Escherichia coli* using various concentrations of quercetin. The results suggest that a frameshift mechanism of mutagenesis is involved. The clear possibility that these naturally occurring and ubiquitous flavonoid compounds may be mutagenic (or carcinogenic) should be investigated in higher organisms. (20 refs)

- 79-0151 Identification of a Mutagenic Substance in a Spice, Sumac, as Quercetin.** (Eng) Seino, Y. (Biochemistry Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan); Nagao, M.; Yahagi, T.; Sugimura, T.; Yasuda, T.; Nishimura, S. *Mutat Res* 58(2/3): 225-229; 1978.

The identification of the mutagenic substance in the spice sumac is reported. The active principle was purified and characterized by thin-layer chromatography, UV-absorption spectroscopy, and mass spectrometry. The mutagenic effects of the purified material and authentic quercetin on *Salmonella typhimurium* strains TA100 and TA98 with and without a rat liver microsomal preparation were similar under every condition tested. The UV absorption spectra of the purified sample from sumac and of authentic quercetin were also the same as was the low-resolution mass spectrum. It is concluded that all the mutagenic activity of sumac is due to quercetin. (16 refs)

- 79-0152 A Simple Solid-Phase Radioimmunoassay for Aflatoxin B₁.** (Eng) Sun, P. S. (Food Res. Inst., Univ. Wisconsin, Madison, WI, 53706); Chu, F. S. *J Food Safety* 1(1): 67-75; 1977.

A solid phase radioimmunoassay for aflatoxin B₁ is described. The method involves the incubation of labeled and unlabeled aflatoxin with IgG-sepharose gel followed by a filtration step. The binding capacity is determined by counting the radioactivity in the filtrate. The results with this method indicate that the technique can be successfully applied to the analysis of small mol wt ligands. Using a simple extraction procedure without clean-up step, the recovery yields of aflatoxin B₁ in contaminated corn or wheat at levels of ≥ 5 ppb were above 60%. (11 refs)

- 79-0153 Reverse Phase High Pressure Liquid Chromatographic Determination of Aflatoxins in Foods.** (Eng) Beebe, R. M. (Food and Drug Admin., 50 United Nations Plaza, San Francisco, CA, 94102). *J Assoc Off Anal Chem* 61(6): 1347-1352; 1978.

A method for determining aflatoxins by high-pressure liquid chromatography (HPLC) with fluorescence detection after CB extraction and cleanup was applied to various foods. Recoveries at 1- to 15-ppb levels from green coffee and peanut butter were 72%-85% and 74%-104%, respectively. The advantages of the HPLC method are speed, precision, sensitivity, selectivity, and immediate chemical confirmation of aflatoxin B₁ and G₁. (18 refs)

- 79-0154 Factors Affecting Formation of Aflatoxin B₁ by *Aspergillus flavus* on Ganga-5 Maize Hybrid**

(Letter to Editor). (Eng) Prakash, O. (Dept. Plant Pathology, Rajasthan Coll. Agriculture, Udaipur, India); Siradhana, B. S. *Curr Sci (Bangalore)* 47(18): 695-696; 1978.

Seeds of hybrid Ganga-5 maize were sterilized, inoculated with *Aspergillus flavus*, and incubated, and conditions optimal for the formation of aflatoxin B₁ (AFB₁) by the mold were determined. AFB₁ formation was max in daylight at a temperature of 25 C, incubation period of 12 days, and relative humidity of 100%. At 25 C and 100% humidity, AFB₁ could be formed within 4 days. (6 refs)

79-0155 Thin Layer Chromatographic Determination of Aflatoxin B₁ in Corn Silage. (Eng) Haggblom, P. E. (Inst. Physiological Botany, Univ. Uppsala, S-751 21 Uppsala 1, Sweden); Casper, H. H. *J Assoc Off Anal Chem* 61(6): 1363-1365; 1978.

Determination of aflatoxin B₁ (AFB₁) in moldy or nonmoldy corn silage by thin layer chromatography (TLC) is described. The toxin is extracted, purified by a combination of cleanup procedures, and analyzed by TLC. The estimated detection limit was 5 µg AFB₁/kg corn silage; 73% of the added AFB₁ was recovered. (9 refs)

79-0156 Aflatoxin Inactivation in Corn by Ammonia Gas: Laboratory Trials. (Eng) Brekke, O. L. (Northern Regional Res. Center, Agricultural Res., Science and Education Admin., U.S. Dept. Agriculture, Peoria, IL, 61604); Stringfellow, A. C.; Peplinski, A. J. *J Agric Food Chem* 26(6): 1383-1389; 1978.

The effect of several process variables on the degree of aflatoxin B₁ (AFB₁) inactivation obtained by treating a stationary bed of corn with a recycling mixture of NH₃ and air was investigated. An NH₃-air mixture was recycled at 25 C through a glass column containing AFB₁-contaminated, shelled corn until a uniform distribution of NH₃ in the corn bed was achieved. After ammoniation and sealed storage at 17.6% moisture and 25 C for 14 days' total reaction time, the AFB₁ level was reduced from 1,000 µg/kg (ppb) to 10 g/kg. The effects of varying the NH₃ level, corn moisture, reaction time, initial AFB₁ level in corn, and recycle gas flow rate were investigated. A pilot-scale experiment wherein 4.86 metric tons of 11% moisture corn was treated with 1.1% of NH₃ reduced the AFB₁ level of the corn from 90 µg/kg to a nondetectable level during 7 mo of storage indoors. Swine feeding tests on this ammoniated corn gave good results. Aqua and gaseous NH₃ appeared equally effective for inactivating the AFB₁ in corn. The data indicate that there is a degree of flexibility among various factors, such as recycle gas flow rate and recirculation time, to achieve a uniform NH₃ distribution throughout the stationary corn bed and between corn moisture and NH₃ level to achieve detoxification. (28 refs)

79-0157 Mycotoxin Producing Potential of Fungi Associated with Dry Shrimps. (Eng) Wu, M. T. (Dept. Nutrition and Food Science, Utah State Univ., Logan, UT, 84322); Salunkhe, D. K. *J Appl Bacteriol* 45(2): 231-238; 1978.

Among 114 fungi isolated from 20 dry shrimp samples (10 showing mold growth and 10 showing no mold growth), 27 isolates (16 *Aspergillus* cultures, 9 *Penicillium* cultures, and chloroform extracts of *Alternaria* and *Cladosporium* species) were toxic to White Leghorn chicken embryos. Ninety-nine of the isolates came from visibly moldy shrimp samples. Visibly moldy dry shrimps had a significantly higher moisture content than nonmoldy samples. *Penicillium* and *Aspergillus* constituted 94% of the total isolates of which *A. ruber* and *P. expansum* were the most common species. Other genera isolated included *Rhizopus*, *Cladosporium*, *Alternaria*, and *Trichothecium*. Although aflatoxins were not detectable on the original samples, 2/3 isolates of *A. flavus*, the most toxic species of *Aspergillus*, were aflatoxin producers. The presence of these quantities and types of mold on commercial shrimp samples could have public health implications. (23 refs)

79-0158 Production of Aflatoxins and Other Fluorescent Metabolites by Strains of *Aspergillus flavus* Isolated from Staple Foods and their Toxicity to Rats. (Eng) Angsubhakorn, S. (Dept. Pathobiology, Faculty Science, Mahidol Univ., Bangkok, Thailand); Bhamarapavati, N.; Romruen, K.; Phienpichit, L.; Thamavit, W.; Sahaphong, S. *Food Cosmet Toxicol* 16(5): 427-430; 1978.

The toxicity of 40 strains of *Aspergillus flavus* isolated from food marketed in Thailand between 1967 and 1969 was examined. Approx 92% of the strains produced aflatoxins B₁ and B₂. Acute toxicity tests in weanling Wistar rats showed that 87.5% of chloroform-extract fractions administered po caused at least one death in test groups of five rats, compared with 38% of petroleum ether-insoluble fractions administered ip. Both fractions produced similar histopathologic lesions in surviving rats. Unidentified compounds that were produced by 18 *A. flavus* strains may have modified the toxic effect of the aflatoxins. (7 refs)

79-0159 Effect of Various Glycolytic and TCA Intermediates on Aflatoxin Production. (Eng) Buchanan, R. L. (Dept. Nutrition and Foods, Drexel Univ., Philadelphia, PA, 19104); Ayres, J. C. *J Food Safety* 1(1): 19-28; 1977.

The effect of various exogenously supplying tricarboxylic acid (TCA) and glycolytic intermediates on aflatoxin production by *Aspergillus parasiticus* was studied with the organism growing in synthetic and semi-synthetic media. At low concentrations, glycerol, lactate, and pyruvate stimulated aflatoxin production in the synthetic medium. At high con-

centrations, pyruvate, citrate, alpha-keto glutarate, fumarate, and malate inhibited aflatoxin accumulation in both media. All supplements except glycerol stimulated sporulation and elevated the pH of the cultures. (12 refs)

- 79-0160 Mutagenicity to *Salmonella typhimurium* of Some *Aspergillus* and *Penicillium* Mycotoxins.** (Eng) Wehner, F. C. (Natl. Res. Inst. Nutritional Diseases South African Medical Res. Council, Tygerberg 7505, South Africa); Thiel, P. G.; Van Rensburg, S. J.; Demasius, I. P. *Mutat Res* 58(2/3): 193-203; 1978.

The mutagenic activity of 17 mycotoxins produced by *Aspergillus* and *Penicillium* species was tested in the Ames' assay using *Salmonella typhimurium* strains, TA98, TA100, TA1535, and TA1537, both with and without a rat liver microsome fraction (S-9) prepared from Aroclor-1254-injected male Wistar-derived rats. The concentrations of the mycotoxins used were determined by preliminary trials and availability. The positive controls aflatoxin B₁, sterigmatocystin and versicolorin A were all mutagenic in the presence of S-9 mix, as were viridicatumtoxin, kojic acid, austocystin A, austocystin D, and austdiol. Austdiol was also mutagenic without rat liver microsome activation. No mutagenic activity was noted for TR₂-toxin, secalonic acid D, penicillic acid, patulin, ochratoxin A, mycophenolic acid, O-methylsterigmatocystin, luteoskyrin, griseofulvin, fumitremorgen B, cyclopiazonic acid, or citrinin. Mutagenic potential seemed to be related to chemical structure, particularly the presence of the bisfuran ring, the xanthone group, and the gamma-pyrone moiety. In general, good agreement was found between existing data on carcinogenicity and mutagenicity determined here, although the carcinogens griseofulvin, luteoskyrin, patulin, and penicillic acid were not mutagenic in this assay. Due to the differing concentrations used, quantitative comparisons of the mutagenic properties of these mycotoxins cannot be made from this study. (46 refs)

- 79-0161 Cell Specificity in Metabolic Activation of Aflatoxin B₁ and Benzo(a)pyrene to Mutagens for Mammalian Cells.** (Eng) Langenbach, R. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Freed, H. J.; Raveh, D.; Huberman, E. *Nature* 276(5685): 277-280; 1978.

The abilities of rat liver cells and rat fibroblasts to metabolize benzo(a)pyrene (BP) and aflatoxin B₁ (AFB₁) to water-soluble products, to intermediates that bind to cellular DNA, and to intermediates that are mutagenic to Chinese hamster V79 cells were studied. BP caused a 17- to 55-fold increase in mutation frequency in V79 cells cocultivated with fibroblasts but no increase in this frequency in V79 cells cocultivated with hepatocytes. AFB₁ caused a 10- to 40-fold increase in mutation frequency in V79 cells cocultivated with hepatocytes and a 2-fold increase in mutation frequency in V79 cells cocultivated with fibroblasts. Hepatocytes metabolized BP

and AFB₁ to water-soluble products, while fibroblasts metabolized BP but not AFB₁. After 24 hr exposure to BP (1 µg/ml), approx three times as much BP was bound to the DNA of the fibroblasts as was bound to the DNA of the liver cells. The data indicate that a cell-type specificity in chemical carcinogenesis can be investigated by the cell-mediated assay and that overall metabolism alone is not sufficient to predict the activity of a carcinogen in a given cell type. (25 refs)

- 79-0162 Improved Colorimetric Method for Determining Nitrate and Nitrite in Foods.** (Eng) Sen, N. P. (Health and Welfare Canada, Food Res. Div., Health Protection Branch, Ottawa, Ontario, Canada K1A 0L2); Donaldson, B. *J Assoc Off Anal Chem* 61(6): 1389-1394; 1978.

A method for determining nitrate and nitrite in cured meat products, cheeses, and vegetables is described. Nitrite is determined colorimetrically by diazotization of sulfanilic acid and subsequent coupling of the product with N-(1-naphthyl)-ethylenediamine. Nitrate is reduced to nitrite on a Cd column and determined similarly. The av recovery of 10-30 ppm of added sodium nitrite was 95%, that of 30-400 ppm of added sodium nitrate 94%. (20 refs)

- 79-0163 Strain Differences in Susceptibility of Rat Colon to 1,2-Dimethylhydrazine Carcinogenesis.** (Eng) Takizawa, S. (Dept. Cancer Res., Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi 1-2-3, Hiroshima 734, Japan); Watanabe, H.; Naito, Y.; Terada, Y.; Fujii, I.; Hirose, F. *Gann* 69(5): 719-722; 1978.

Susceptibility to 1,2-dimethylhydrazine (DMH) carcinogenesis was compared in two rat strains, Wistar-Furth (WF) rats derived from a substrain prone to colon cancer and Long-Evans (LE) rats. Ten-week-old rats were injected with 20 mg/kg DMH weekly for 20 wk and sacrificed at weeks 10, 15, 20, and 25 after the last injection. The incidence of benign and malignant colon tumors and the number of tumors per rat were higher in LE rats. Most of the colon tumors occurred in the descending colon, where only a few tumors were found in WF rats. Autoradiographic studies did not show any apparent difference between the two rat strains (both DMH-treated and untreated controls) in the number of ³H-thymidine-labeled cells or in the number of mitotic cells in the mucosa of the descending colon. It is likely that a resistant rat strain (WF) for DMH carcinogenesis has emerged. (11 refs)

- 79-0164 Metabolism of Hydrazines and Hydrazides by the Intestinal Microflora.** (Eng) Bolton, G. C. (Dept. Biochemistry, Univ. Birmingham, Birmingham B15 2TT, England); Griffiths, L. A. *Experientia* 34(11): 1484-1486; 1978.

The ability of rat intestinal microflora to degrade a number of hydrazines and hydrazides during anaerobic incubation in vitro was examined. Medium containing 0.36 mg/ml hydrazo-substituted compound and microflora was incubated for 7 days and the inoculated media centrifuged. The supernatants were filtered and submitted either directly or following a dansylation reaction to thin-layer chromatography. All of the hydrazine compounds gave rise, by reductive fission, to primary amines. The hydrazides apparently did not undergo reductive fission, since none of the expected fission products were detected. There was no evidence of the formation of hydrazide hydrolysis products. These experiments indicate that under in vitro conditions, intestinal microflora is able to effect extensive reductive fission of hydrazines, but the extent to which this would occur in vivo must be assessed by studies in intact animals. (16 refs)

- 79-0165** Mutagenic Activity of Furfural in *Salmonella typhimurium* TA100. (Eng) Zdzienicka, M. (Dept. Biochemistry, Warsaw Medical Sch., Banacha 1, 02-097, Warsaw, Poland); Tudek, B.; Zielenska, M.; Szymczyk, T. *Mutat Res* 58(2/3): 205-209; 1978.

The mutagenicity of furfural, a widely used solvent, was tested in the Ames' mutagenicity assay using *Salmonella typhimurium* strains TA100 and TA98, both with and without liver microsome S-9 mix prepared from Aroclor-1254-treated Wistar rats. Furfural was mutagenic in the TA100 strain: as a dose of 7 μ l/plate doubled the number of revertants; however, doses > 7 μ l/plate decreased the number of revertant colonies, due to the appreciable cellular toxicity of furfural. In fact, when toxicity was taken into account, the number of revertant colonies, per 10⁶ surviving cells was increased nine times by 7 μ l furfural. Furfural was not mutagenic toward strain TA98, and did not appear to be metabolically activated by the microsomal fraction of the rat liver. Because of suspected co-carcinogen activity, furfural was assayed with TA100 in the presence of 5 μ g/plate benzo(a)pyrene (BP). Although cellular toxicity was decreased, the curves for mutagenesis by furfural in the presence and absence of BP were similar, indicating that the mutagenic activity of furfural was not increased by the presence of BP. (8 refs)

- 79-0166** Mutagenic Effects of Thioacetamide in *Drosophila melanogaster*. (Eng) Magnusson, J. (Environmental Toxicology Unit, Wallenberg Lab., Univ. Stockholm, Stockholm, Sweden); Ramel, C. *Mutat Res* 58(2/3): 259-262; 1978.

The mutagenicity of thioacetamide was tested in *Drosophila melanogaster*. Thioacetamide was administered to 2-day old males either intra-abdominally (500 ppm or 100 ppm) or po (2,500 ppm). After treatment the males were individually mated and mutagenicity determined by the sex-linked recessive lethal test in heterozygous daughters from this mating.

In all three experiments there was a significant increase of lethals in the thioacetamide-treated series compared with controls. The different dosages used in the injection experiments did not reveal any dose-effect relationship for mutagenicity; the frequency of lethals was lower with the higher than with the lower dose (0.19% and 0.28%, respectively). In the feeding experiment, the percentage of lethals was 0.22% compared to 0.05% for controls. It is concluded that thioacetamide is a mutagen, a result that correlates with its carcinogenicity in mice and rats. (14 refs)

- 79-0167** Mitogenic and Carcinogenic Effects of a Hypolipidemic Peroxisome Proliferator, [4-Chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic Acid (Wy-14,643), in Rat and Mouse Liver. (Eng) Reddy, J. K. (G. D. Searle & Co., P. O. Box 5110, Chicago, IL, 60680); Rao, M. S.; Azarnoff, D. L.; Sell, S. *Cancer Res* 39(1): 152-161; 1979.

The effects of [4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]-acetic acid (Wy-14,643), a potent hepatic peroxisome proliferator, on male acatalasemic CS-b mice and F344 rats were investigated. Wy-14,643 was incorporated in the diet at a level of 0.1% for 16 mo (15 rats) or at a level of 0.1% for 6 mo and then 0.05% for 8.5 mo (20 mice). All 18 surviving mice developed multiple liver tumors, most of which were of the trabecular type. Vascular invasion was encountered frequently in these tumors. All 15 rats developed hepatocellular carcinomas with trabecular patterns. Metastases to the lungs were present in five mice and six rats. Peroxisomes were prominent in the tumors, and several of these organelles contained prominent nucleoids. The carnitine acetyltransferase activity in the primary hepatocellular carcinomas was markedly increased, but catalase activity in the tumors was not inducible. In a short-term study, liver wt, liver DNA, and specific radioactivity of labeled DNA increased in rats fed 0.125% Wy-14,643 for 5 days. There was no evidence of hepatocellular necrosis. Elevations in serum alpha-feto-protein concentration were associated with and proportional to liver cell proliferation. The data prompt concern over the potential carcinogenicity of hepatic peroxisome proliferators as a class. (52 refs)

- 79-0168** Interaction of Glyoxal with Glycine and N-Methylacetamide: Some Aspects of Their Potential Energy Surface and Its Relation with Cancer. (Eng) Del Conde, G. (Division de Estudios Superiores, Facultad de Quimica, Universidad Nacional Autonoma de Mexico, Mexico 20, D.F.); Estrada, M.; Cardenas, A. *Int J Quant Chem Quant Biol Symp* (5): 393-401; 1978.

The interactions of cis- and trans-glyoxal and glycine as a prototype of the carboxylic end of a protein, and the interaction of glyoxal and N-methylacetamide as a prototype of a peptide bond were investigated. Part of their potential energy

surface was obtained by the CNDO/2 approximation. The action of trans- and cis-glyoxal was shown to be completely different in a model of a carboxylic end of a protein, suggesting that cis-glyoxal should not have any effect as a "brake" in protein biosynthesis. Analysis of a peptide-bond model suggested that both glyoxal isomers should behave in a similar way. (9 refs)

79-0169 Inhibition of In Vitro Metabolic Activation of Carcinogens by Wheat Sprout Extracts. (Eng)

Lai, C. N. (Dept. Biology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77025); Dabney, B. J.; Shaw, C. R. *Nutr and Cancer* 1(1): 27-30; 1978.

When tested in the Ames' mutagenicity assay with *Salmonella typhimurium* strain TA100 and S-9 rat liver homogenate fraction, extracts from the leaves and roots of 7- to 14-day-old wheat sprouts were able to inhibit the mutagenicity of 2-acetylaminofluorene (50 µg/plate), N-hydroxy-2-acetylaminofluorene (5 µg), 3-methylcholanthrene (25 µg), 2-aminoanthracene (0.3 µg), benzo(a)pyrene (BP: 5 µg), and aflatoxin B₁ (0.1 µg), compounds known to require metabolic activation. The degree of mutagenic inhibition was dependent upon the dose of sprout extract (25-150 µl). Carcinogens that do not require metabolic activation (2-nitrofluorene, ethyl methanesulfonate, and N-methyl-N'-nitro-N-nitrosoguanidine) were not inhibited by sprout extracts. High-pressure liquid chromatographic profiles of the BP metabolites showed that dihydrodiols were reduced significantly, particularly by the root extracts. Mung bean and lentil sprouts demonstrated inhibition similar to that of the wheat sprouts. Analysis of the wheat sprouts suggested that the active component is a heat-sensitive protein or protein-bound entity with a mol wt > 100,000. The extracts were inhibitory at relatively low levels and they were nontoxic, even at high levels, unlike most other known mutagenicity inhibitors. (24 refs)

79-0170 Structural Evidence on DNA Carcinogen Interactions. N-Acetoxy-2-acetylaminofluorene Binding to DNA. (Eng)

Norden, B. (Dept. Inorganic Chemistry, Univ. Lund, Chemical Center, P.O. Box 740, S-220 07 Lund, Sweden). *Biophys Chem* 8(4): 385-391; 1978.

The interaction between N-acetoxy-2-acetylaminofluorene (AAAF) and calf thymus DNA was studied by a linear dichroism (LD) measuring technique. In a low-ionic-strength 50% methanol solvent at room temperature, only a weak complex (van der Waals) appeared. However, when a "sodium-free" sample was heated to < 40 C, strand separation was observed and a covalent aminofluorene complex formed. After the sample was cooled to room temperature, a characteristic positive LD band was observed at 306 nanometers (nm). The temperature effect was clearly related to denaturation or par-

tial denaturation. The average angular orientation of the long axis of the fluorene moiety (47 degrees to the local helix axis) was inconsistent with intercalation. It could be explained by a free rotation around a C(DNA)-N(aminofluorene) bond or by a major groove site. The occupation density was 1 to 2 aminofluorene residues per 100 bases. With native DNA, AAAF slowly formed a covalent complex that had a negative LD at 307 nm. The orientation (70-90 degrees) was consistent with steric direction by the strand. (17 refs)

79-0171 Sister-Chromatid Exchanges Induced in Rabbit Lymphocytes by 2-Aminofluorene and 2-Acetylaminofluorene after In Vitro and In Vivo Metabolic Activation. (Eng)

Takehisa, S. (Lab. Radiobiology, Univ. California, San Francisco, CA, 94143); Wolff, S. *Mutat Res* 58(2/3): 321-329; 1978.

The sister-chromatid exchanges (SCE) induced in rabbit peripheral lymphocytes by 2-aminofluorene (2-AF) and 2-acetylaminofluorene (2-AAF) were examined after in vivo and in vitro metabolic activation. Female New Zealand rabbits received (7, 50, or 200 mg/kg ip) or 2-AAF (3, 10, 50, 100, or 200 mg/kg ip) and blood was drawn for culture 1, 2, 3, and 7 days later. In rabbits injected with 2-AF, a transient dose-dependent increase in SCE was seen in peripheral lymphocytes cultured after stimulation with phytohemagglutinin (PHA). With 2-AAF, the response was more variable: some rabbits showed an increase in SCE immediately, but one showed an increase only after a subsequent injection. For the in vitro tests, blood drawn from three rabbits before they had received any injections was treated with the test chemicals and S-9 mix (rat-liver microsomes supplemented with an NADPH-generating system) for 30 min either just before culturing in PHA-containing medium or before addition of bromodeoxyuridine (BrdUrd). With 2-AF and S-9 mix treatment, there was no increase in SCE frequency unless the treatment occurred after PHA stimulation. Exposure for 30 min to 2-AAF and the metabolic activation system did not increase the yield of SCE at any time of culture. However, prolonged exposure of the cells to 2-AF or 2-AAF alone during the period of BrdUrd incubation after PHA stimulation increased the number of SCE. These results indicate that the addition of PHA and the consequent metabolic activation do affect the induction of enzymes involved in the activation of 2-AF and 2-AAF. (21 refs)

79-0172 Studies on the Mutagenicity of N-Hydroxy-2-acetylaminofluorene in the Ames-Salmonella Mutagenesis Test System. (Eng)

Andrews, L. S. (Pharmacology-Toxicology Program, Natl. Inst. General Medical Sciences, NIH, Bethesda, MD, 20014); Hinson, J. A.; Gillette, J. R. *Biochem Pharmacol* 27(20): 2399-2408; 1978.

N-hydroxy-2-acetylaminofluorene (NOH-2AAF) was

deacetylated by Sephadex G-25-chromatographed postmitochondrial supernatant fraction to a substance (presumably N-hydroxy-2-aminofluorene) that was a potent frameshift mutagen in the Ames-Salmonella tester strain TA1538. Preincubation of the supernatant fraction with paraoxon decreased the observed mutagenesis; however, the addition of several reducing agents or nucleophiles to the incubations did not alter the mutagenic response. Sulfation of NOH-2AAF decreased the mutagenesis observed under conditions of supernatant activation and increased the covalent binding of [¹⁴C-acetyl]NOH-2AAF to protein. Under conditions of N-O-sulfate ester generation, ascorbate or reduced pyridine nucleotides greatly increased the number of revertant colonies. Ascorbate did not alter the rate of sulfation of NOH-2AAF, but it decreased the protein covalent binding and greatly increased the reduction of the arylating species to 2-acetylaminofluorene (2AAF). Since 2AAF was not mutagenic under these conditions, the data are consistent with the concept of a free radical of 2AAF as the mutagenic intermediate. (32 refs)

79-0173 A Sub-population of Rat Liver Membrane-bound Ribosomes That are Detached In Vitro by Carcinogens and Centrifugation. (Eng) Palmer, D. N. (Dept. Biochemistry, Univ. Coll. London, Gower St., London WC1E 6BT, England); Rabin, B. R.; Williams, D. J. *Biochem J* 176(1): 9-14; 1978.

The chemical-carcinogen-induced detachment of ribosomes from Sprague-Dawley rat liver endoplasmic reticulum was studied in vitro. Incubation of postmitochondrial supernatant with 0.2 mM diethylnitrosamine or N-2-acetylaminofluorene removed approx 16% of membrane-bound ribosomes, measured as differences in RNA/protein values of membrane separated from unbound ribosomes by flotation. These ribosomes are also detached by exposure to high centrifugal forces (160,000 g) and are among those removed by NADPH-catalyzed lipid peroxidation. The ribosomes (polyribosomes) removed are not those detached from the membrane by exposure to high KCl concentrations (loosely bound) or high KCl concentrations in the presence of puromycin (tightly bound). It is concluded then that centrifugally labile and carcinogen-sensitive ribosomes represent a previously unreported subpopulation of membrane-bound ribosomes. (30 refs)

79-0174 Hematogenous Development of Rat Mature Granulocytic Leukemia. Distribution of Leukemic Foci in Vertebral Bodies. (Eng) Takayama, S. (Dept. Pathology, Faculty Medicine, Tokyo Medical and Dental Univ., Tokyo, Japan); Fujiwara, M. *Acta Pathol Jpn* 28(5): 663-668; 1978.

The distribution of leukemic foci in the vertebrae of Wistar rats with N,N'-2,7-fluorenylenebisacetamide (2,7-FAA)-in-

duced or transplanted leukemias was studied. The leukemic foci in the bone marrow were small, circumscribed, and nodular, and there was little or no leukemic infiltration of the spleen or liver. In both the induced and transplanted leukemias, the leukemic foci were most frequently located around the center of the craniocaudal axis, but they were distributed evenly along the dorsoventral axis. The similar infiltration patterns of the 2,7-FAA-induced and transplanted leukemias suggests a similar mode of spread. 2,7-FAA-induced mature granulocytic leukemia may be spread by hematogenous metastasis from primary nodular foci in the bone marrow to other parts of the bone marrow. (13 refs)

79-0175 Rat Liver Aldehyde Dehydrogenase--Immunochemical Identity of 2,3,7,8-Tetrachlorodibenzo-p-dioxin Inducible Normal Liver and 2-Acetylaminofluorene Inducible Hepatoma Isozymes. (Eng) Lindahl, R. (Developmental Biology Section, Dept. Biology, Univ. Alabama, University, AL, 35486); Roper, M.; Deitrich, R. A. *Biochem Pharmacol* 27(20): 2463-2465; 1978.

Aldehyde dehydrogenase (ALDH) isozymes in 2-acetylaminofluorene-induced rat hepatomas were studied immunochemically. In Ouchterlony immunodiffusion assays, rabbit antisera against 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced normal liver ALDH α and τ isozymes formed precipitin lines with hepatoma-specific α isozymes. Hepatoma-specific antibody against hepatoma-specific α isozyme reacted with complete identity with normal liver TCDD-induced τ isozyme. Neither anti- α nor anti- τ serum reacted with phenobarbital-induced rat liver ALDH ϕ isozyme. Thus, the α and τ isozymes are not related immunochemically to the ϕ isozyme. (21 refs)

79-0176 Growth Stimulation Following Serum Transfer from Carcinogen-treated Donors to Normal Rats: a New Aspect of Early Carcinogen Actions. (Eng) Danz, M. (Pathologisches Institut, Friedrich-Schiller-Universität, Ziegmühlenweg 1, DDR-69 Jena, E. Germany); Urban, H.; Brauer, R.; Schmidt, A. *Exp Pathol (Jena)* 16(1-6): 23-35; 1978.

The effects of treatment with 2-acetylaminofluorene (AAF, 120 mg/kg by stomach tube) or with the serum of AAF-treated animals (1.5 ml/g) on growth of the liver, adrenals, esophageal epithelium, and jejunal crypts were studied in male Sprague-Dawley rats. Serum was taken from AAF-treated donors sacrificed 9, 14, or 24 hr after treatment. Liver wts were elevated in rats treated with serum taken 9 or 14 hr after AAF treatment. A mild inflammatory response in the portal fields was seen 24 hr after AAF treatment, but there were no abnormalities in animals treated with serum. The hepatic mitotic index decreased significantly with time in the AAF-treated rats and increased significantly in serum-treat-

ed rats, especially at 28 hr after injection. The adrenal mitotic index was decreased 14 hr after AAF treatment and was increased after serum treatment. The stimulatory activity of the serum was limited to the outer and middle layers of the zona fasciculata of the adrenal cortex. The mitotic indices of the esophageal epithelium and jejunal crypts were not influenced by AAF or serum treatment. Serum from AAF-treated animals had an in vitro stimulatory effect on thymocytes. (66 refs)

- 79-0177 Morphometric Investigations on Endocrine Glands. IV. The Rat Thyroid During Liver Regeneration after Partial Hepatectomy with and Without Application of Carcinogenic Substances.** (Eng) Low, O. (Pathologisches Institut, Friedrich-Schiller-Universitat, DDR-69 Jena, Zieglmuhlenweg 1, E. Germany); Richter, S.; Franke, I.; Danz, M. *Exp Pathol (Jena)* 16(1-6): 234-244; 1978.

Histologic changes in the thyroid gland during regeneration after partial hepatectomy and the effects of pretreatment with acetylaminofluorene (AAF, 55 mg/kg/day for 3 days) or methylnitrosourea (MNU, 12 mg/kg/day for 3 days) were studied using male Wistar and Sprague-Dawley rats. The thyroids of laparotomized controls histologically resembled those of untreated rats. Those of hepatectomized rats were characterized by follicles that were reduced in size and contained less colloid. The relative percentages of epithelium increased by day 3 after hepatectomy and were particularly marked by day 10. The percentage of mitoses was lower than that in controls. AAF decreased the relative amount of thyroid epithelium before and after hepatectomy and increased the relative amount of colloid. MNU had a similar effect when followed by hepatectomy, but it had no effect alone. The results suggest that regeneration resulted in activation of the thyroid and that thyroid hormones may influence carcinogenesis and vice versa. (74 refs)

- 79-0178 Nitrite Formation from 2-Nitropropane by Microsomal Monooxygenases.** (Eng) Ullrich, V. (Dept. Physiological Chemistry, Physiologisch-chemisches Institut, Universitat des Saarlandes, 665 Homburg-Saar, W. Germany); Hermann, G.; Weber, P. *Biochem Pharmacol* 27(19): 2301-2304; 1978.

In the presence of NADPH and dioxygen, Sprague-Dawley rat liver microsomes catalyzed the oxidative denitrification of 2-nitropropane to acetone and nitrite. Pretreatment of the animals with phenobarbital and 3-methylcholanthrene increased the specific activity. Inhibitors of microsomal monooxygenases inhibited nitrite formation, and the photochemical action spectrum of the CO-inhibited reaction indicated the involvement of cytochrome P450. The Km value and the spectral dissociation constant, Ks, of the substrate binding spectrum were both around 10^{-2} M. 1-Nitropropane

also undergoes oxidative denitrification. It is suggested that aliphatic nitro compounds may have mutagenic or carcinogenic effects, as recently demonstrated for 2-nitropropane in rats. (21 refs)

- 79-0179 Determination of Radiation Equivalence of the Chemical Furfurylamine (AF-2) for the Induction of Gene Conversion in Diploid Yeast and Estimation of Genetic Risk to the Japanese Population.** (Eng) Murthy, M. S. (Div. Radiological Protection, Bhabha Atomic Res. Centre, Trombay, Bombay-400 085, India); Sankaranarayanan, N. *Mutat Res* 54(3): 323-331; 1978.

Dose-effect relationships for the induction of gene conversion by furfurylamine (AF-2) in diploid yeast were established and used to determine the radiation equivalence (rec) value for AF-2 and the genetic risk to the Japanese population arising from its consumption. The rec value, calculated by taking the ratio of the slopes of the dose-effect curves to gamma radiation to that of AF-2, was determined to be $0.085 \mu\text{g/ml/hr}$. This value was remarkably consistent with the rec values previously obtained in different test systems and with different end-points. The genetic burden to the Japanese population due to consumption of AF-2 was estimated to be equivalent to 55 millirec. However, uncertainties in the consumption of AF-2 per person and in its metabolic detoxification tend to lower the probable value to a small fraction of that due to natural background ionizing radiation (average, 100 mrem/yr). (18 refs)

- 79-0180 Chromosome Breakage and Neoplastic Transformation of Syrian Golden Hamster Embryonic Cells in Tissue Culture by Transplacental Application of 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2).** (Eng) Inui, N. (Section Cell Biology, Cytogenetics, Biological Res. Inst., Japan Tobacco and Salt Public Corporation, Hatano, Kanagawa 257, Japan); Nishi, Y.; Taketomi, M. *Mutat Res* 58(2/3): 331-338; 1978.

On day 11 or 12 of gestation, Syrian golden hamsters were injected ip with 0.5 ml dimethyl sulfoxide containing 20, 50, or 100 mg/kg 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2). Embryos were isolated 24 hr later, cultured, and examined for the carcinogenic and mutagenic effects of transplacental exposure to AF-2. Within the first 24 hr of primary culture, cells were treated with colcemide for 3 hr so that mitotic cells could be observed in the first cell cycle in vitro. Cultured embryonic fibroblasts in metaphase plates showed a marked dose-dependence in chromosome aberrations. Transplacental application of AF-2 also caused a slightly dose-dependent morphological transformation. When transformed colonies were cloned and transferred to the hamster cheek pouch, these cells produced tumors in the host animals. This new in vivo-in vitro combination assay system should

be useful in detecting potential environmental carcinogens. (26 refs)

- 79-0181** Determination of Ethanolamines and N-Nitrosodiethanolamine in Commercial Cutting Fluids by Gas Chromatography and Mass Fragmentography. (Jpn) Kawano, M. (Dept. Environmental Conservation, Coll. Agriculture, Ehime Univ., 3-5-7, Tarumi, Matsuyama-shi, Ehime, Japan); Wakimoto, T.; Tatsukawa, R. *Bunseki Kagaku* 27(10): 616-621; 1978.

A method for simultaneous determination of ethanolamines and N-nitrosodiethanolamine (ND) in commercial cutting fluids was developed. A sample (about 10 mg) is taken into a test tube with a cap and then ethanol (1 ml), urea (2%, 0.5 ml), and acetic acid (0.1 ml) are added to destroy the nitrite that is usually present in a sample. After being shaken slowly, the mixture is dried by heating under a stream of nitrogen gas. Ethanol (about 1 ml) is added to the residue, which is dried until it does not smell of acetic acid, and is silylated in an oil bath for 10 min with dimethylformamide (200 μ l) and N,O-bis(trimethylsilyl)trifluoroacetamide (200 μ l) at 60 C. The silylated soln is diluted with dimethylchloride, and an aliquot is injected into the gas chromatograph. Some selected mass numbers (mass/electric charge) of ethanolamines (mono, di, and tri) and ND are 102, 130, 262, and 130. Through the analytical process, artifact formation of ND was not observed. The detection limit for ethanolamines (mono, di, and tri) and ND by mass fragmentography were 1, 1, 1, and 5 nanog, and by gas chromatography were 4, 2, 2, and 4 μ g, respectively. (8 refs)

- 79-0182** A Possible Short-Term Prediction of Potential Carcinogenicity of Chemical Compounds In Vivo by Means of a Promoting Activity Test (PAT). (Eng) Danz, M. (Pathologisches Institut, Friedrich-Schiller-Universitat, DDR-69 Jena, Ziegmuhlenweg 1, E. Germany); Urban, H.; Schmidt, A.; Ziebarth, D. *Exp Pathol (Jena)* 16(1-6): 109-120; 1978.

Carcinogens of chemically unrelated structure and different organotropism stimulated mitosis in the adrenocortical cells of Sprague-Dawley and Wistar rats and Syrian golden hamsters in vivo. The animals were given a single dose of approx 15%-30% of the LD₅₀ of each substance, mainly by stomach tube, and sacrificed 48 hr later. A similar response was observed in the regenerating liver of rats following partial hepatectomy or intoxication by carbon tetrachloride. This relatively rapid response was probably due to the emergence of humoral growth stimulators that are evidenced in restorative regeneration, and it probably accounts for the promoting activity of carcinogens. Special problems resulting from false-positive (indomethacin, sodium nitrite) and false-negative (7,12-dimethylbenz(a)anthracene, ethionine) findings as well as the role of solvents are discussed. The agreement be-

tween the results of this short-term test and long-term carcinogenicity tests of trinitrosotrimethylenetriamine, nitrosoethyl-tert-butylamine, and nitrosodiallylamine illustrates the accuracy of the former for predicting the carcinogenicity of chemical compounds. (65 refs)

- 79-0183** Enhancing Effect of Partial Pancreatectomy and Ethionine-induced Pancreatic Regeneration on the Tumorigenesis of Azaserine in Rats. (Eng) Denda, A. (Dept. Oncological Pathology, Cancer Center, Nara Medical Univ., 840 Shijo-cho, Kashihara, Nara-ken 634, Japan); Inui, S.; Sunagawa, M.; Takahashi, S.; Konishi, Y. *Gann* 69(5): 633-639; 1978.

The effect of partial pancreatectomy (PP) or a protein-deficient diet containing 0.5% ethionine (ethionine diet: ED) on the pancreatic tumorigenesis of azaserine (AZ) was studied in Wistar rats. Adenomas of the nonendocrine pancreas were induced in 100% of rats in all AZ-treated groups at 62 wk. The size and number of the adenomas were significantly increased in rats of the PP and ED groups, compared with those in the control group. Although there was no significant difference in the number of adenomas in rats treated by PP pancreatectomy and those given the ED, the size of the tumors was significantly larger in the PP rats than in the ED rats. These results indicate that pancreatic tumorigenesis by AZ was enhanced by both the regeneration induced by PP and the ingestion of the ED; however, the enhancing effect of PP was greater than that of the ED. (23 refs)

- 79-0184** In Vivo Autoradiography and Nitrosoheptamethyleneimine Carcinogenesis in Hamsters. (Eng) Reznik-Schuller, H. (Chemical Carcinogenesis Program, NCI-Frederick Cancer Res. Center, Frederick, MD, 21501); Lijinsky, W. *Cancer Res* 39(1): 72-74; 1979.

This study is part of a series of morphological and biochemical investigations of the pronounced organotropic effects of some nitrosamines. Quantitative autoradiograms were made, in vivo, in European hamsters with the use of a single dose of [¹⁴C]nitrosoheptamethyleneimine (NHMI: 260 μ Ci/animal; time between intragastric administration of nitrosamine and killing of animals, 6 hr). The animals had been given weekly sc injections of unlabeled NHMI at 0.20 of the dose lethal to 50% of the animals (33 mg/kg). In this species, the lung is the principal target, and radioactivity was found in the Clara cells of the bronchial epithelium and in the NHMI-induced tumors derived from these cells. Tumors were not induced in the liver, which can metabolize this compound, and labeling was found principally in the cytoplasm of liver cells. In the target cells, however, there was a high degree of labeling in both the cytoplasm and the nuclei. (12 refs)

- 79-0185 Electronic Structure of Biopolymers and Possible Mechanisms of Chemical Carcinogenesis.** (Eng) Ladik, J. (Lehrstuhl für Theoretische Chemie, Friedrich-Alexander-Universität Erlangen-Nürnberg, 8520 Erlangen, W. Germany); Suhai, S.; Seel, M. *Int J Quant Chem Quant Biol Symp* (5): 35-49; 1978.

The results of a coherent potential approximation calculation using k - and energy-dependent self-energy are presented for a polymer, namely, the (SN) x and (SN-H) x mixed system. In addition, band structures for polyglycine are presented. On the basis of information concerning the electronic structures of these biopolymers, possible mechanisms of action of different carcinogens bound to DNA and/or proteins are discussed. (42 refs)

- 79-0186 Conduction in Protein and Methylglyoxal-Protein Complexes.** (Eng) Lewis, T. J. (Univ. Coll. North Wales, Bangor, Gwynedd, Wales). *Int J Quant Chem Quant Biol Symp* (5): 149-158; 1978.

A model for the dielectric and conductive behavior of proteins and protein-methylglyoxal complexes based on thermally activated hopping (or charge carrier motion) is presented. It appears that this model gives a reasonable interpretation of a wide range of electrical measurements on the proteins, especially when they are complexed with methylglyoxal. (18 refs)

- 79-0187 Application of High Performance Liquid Chromatography for the Determination of N-Nitrosodialkylamines.** (Jpn.) Hirayama, T. (Kyoto Coll. Pharmacy, Misasagi, Yamashina-ku, Kyoto, Japan); Kiuchi, T.; Fukui, S. *Shokuhin Eiseigakuzasshi* 19(5): 468-473; 1978.

High performance liquid chromatography proved to be faster and easier than other methods for the determination of N-nitrosamines. Sensitivity was 0.05 nanog, and the recoveries of all but one of the N-nitrosamines tested (N-nitrosodimethylamine) were over 99%. (20 refs)

- 79-0188 Estimation of Extractable N-Nitroso Compounds at the Parts-per-Billion Level.** (Eng) Drescher, G. S. (Ciba-Geigy Corp., Development Dept., McIntosh, AL); Frank, C. W. *Anal Chem* 50(14): 2118-2121; 1978.

A rapid (< 1 hr) preliminary screening method for estimating the total N-nitroso group content in a wide variety of environmental samples is described. The samples are extracted with methylene chloride and back-extracted with distilled-deionized water to remove nitrite. The extract is dried over anhydrous sodium sulfate, concentrated, and subjected to

acid-catalyzed denitrosation using 0.2 ml of 0.56 M HBr in glacial acetic acid. The nitric oxide that evolves is detected via its chemiluminescence reaction with ozone. The detection limits are < 10 ppb for most N-nitroso compounds, which permits the use of original sample sizes as low as 10 g. The selectivity of the method is excellent, with the only serious interferences being due to sodium nitrite and alkyl nitrites, although their molar response values are considerably lower than those obtained for the same concentrations of N-nitroso derivatives. The detection system responds on an equimolar basis to a wide range of different N-nitroso compounds with a precision of $\pm 5\%$. Application of the method to 100-g samples of water, soil, and urine spiked with approx 1 μ of N-nitroso compound is described. (29 refs)

- 79-0189 Determination of Nitrite at Low Level Without Prior Extraction.** (Eng) Walters, C. L. (British Food Manufacturing Industries Res. Assoc., Leatherhead, Surrey, England); Downes, M. J.; Hart, R. J.; Perse, S.; Smith, P. L. *Z Lebensm Unters Forsch* 167(4): 229-232; 1978.

A procedure that permits the determination of low levels of sodium nitrite in food or other dried matrices without prior extraction is described. Nitric oxide released from nitrite through the action of acetic acid is determined by a chemiluminescence analyzer. The detection limit is approx 0.02 μ g. Although the method is most suitable for use with dry materials, the response from a wet sample could be monitored through subsequent injection of a standard aliquot of nitrite in a minimum volume of water. (10 refs)

- 79-0190 Effects of Cytochrome P-448 and P-450 Inducers on Microsomal Dimethylnitrosamine Demethylase Activity and the Capacity of Isolated Microsomes to Activate Dimethylnitrosamine to a Mutagen.** (Eng) Guttenplan, J. B. (Dept. Biochemistry, New York Univ. Coll. Dentistry, New York, NY, 10010); Garro, A. J.; Hutterer, F. In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 139-153; 1977.

The relationship between dimethylnitrosamine demethylase (DMN DMase) and the activation of DMN mutagenicity was analyzed through the use of three types of microsomal enzyme inducers, phenobarbital (PB), 3-methylcholanthrene (3-MC), and Aroclor 1254. The microsomes were prepared from male C57 and DBA/2 mice. Activation of DMN to a mutagen was assayed by a bacterial auxotroph reversion test using the His- *Salmonella typhimurium* strain TA1530. Aminopyrine DMase and benzo(a)pyrene (BP) hydroxylase activities were also monitored as representative of enzymes that are primarily cytochrome P-450- and P-448-dependent,

respectively. With C57 mice, all three inducers produced significant increases in DMN DMase and mutagenic activities. The capacity of microsomes from all treated animals to convert DMN to a mutagen was increased to a greater extent than their capacity to demethylate DMN. With DBA/2 mice, 3-MC was ineffective; the response to PB was normal and that to Aroclor 1254 was reduced compared with the responses of C57 mice. SKF 525-A inhibited mutagenic activation and the enzyme activities of 3-MC induced and control microsomes, particularly the latter. BP was more effective in inhibiting mutagenic activation and the enzyme activities of 3-MC-induced and control microsomes, particularly the latter. In all cases, mutagenesis was inhibited to a greater extent than the enzyme activities. Cytochromes P-450 and P-448 may contribute to DMN DMase and mutagenicity, and high levels of both cytochromes may be necessary for efficient activation of DMN to a mutagen. (33 refs)

- 79-0191 The Phosphorylation of Rat Liver Ribosomes Following Administration of Dimethylnitrosamine.** (Eng) Gressner, A. M. (Dept. Clinical Chemistry, Medical Faculty RWTH, Aachen, W. Germany); Greiling, H. *Biochem Pharmacol* 27(21): 2495-2498; 1978.

The effect of dimethylnitrosamine (DMNA) administration on liver ribosomal protein phosphorylation was studied in male Sprague-Dawley rats. The animals were injected ip with 30 mg/kg DMNA and at 2 and 5 hr later with 0.8 mCi carrier-free (32 P)-orthophosphoric acid. The rats were killed 30 min later. The incorporation of (32 P)phosphate into the 40S ribosomal subunit was stimulated five- and nine-fold at 2 and 5 hr, respectively, after administration of the drug. The phosphorylation of the 60S ribosomal subunit was not affected. The enhanced phosphorylation of the 40S subunit was due to a 20-fold stimulated incorporation of phosphate into only one ribosomal protein, S6. The functional significance of this type of postsynthetic modification of the 40S subunit is difficult to assess since the role of protein S6 and of its phosphorylated derivative S6P in the mechanism of peptide chain synthesis is not clear. It is speculated that S6 and S6p may influence the selection of specific messenger RNAs by the 40S subunit and thus influence the qualitative regulation of protein synthesis on the translational level. (36 refs)

- 79-0192 Somatic Crossing-Over in Glycine Max (L.) Merrill: Activation of Dimethyl Nitrosoamine by Plant Seed and Comparison with Methyl Nitrosoarea in Inducing Somatic Mosaicism.** (Eng) Arenaz, P. (Program in Genetics, Washington State Univ., Pullman, WA, 99163); Vig, B. K. *Mutat Res* 52(3): 367-380; 1978.

The potential of dimethylnitrosamine (DMN) to cause somatic mosaicism was studied in a *Glycine max* (soybean) test system and compared with that of methyl nitrosoarea (MNU). In this system, DMN was activated by plant seeds

to a true mutagen without the addition of NADPH or the S-9 fraction of rat liver homogenate. Mosaicism was induced with a dose as low as 1.25 ppm DMN, with the upper limit for spot production being reached at 60 ppm. MNU, which does not require activation, did not show a limitation. The frequency of twin spots on $Y_{11}y_{11}$ leaves was increased only slightly by DMN or MNU, suggesting a small increase in somatic crossing-over. Neither chemical could mutate y_{11} to Y_{11} . (35 refs)

- 79-0193 Inhibition of Rat Hepatic Dimethylnitrosamine Demethylase by Cyclic and Acyclic Nitrosamines and Secondary Amines.** (Eng) Chau, I. Y. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139); Archer, M. C. *Experientia* 34(11): 1505-1506; 1978.

The inhibition of hepatic dimethylnitrosamine (DMN) demethylase by a number of cyclic and acyclic nitrosamines and secondary amines was investigated using male albino Sprague-Dawley rats. The animals were pretreated for 7 days with 0.1% phenobarbital po and then sacrificed. Rat liver microsomes were incubated for 5 min before the addition of DMN (102 mM) and various concentrations of inhibitor. All of the nitrosamines examined, both acyclic and cyclic, produced a concentration-dependent inhibition of hepatic DMN metabolism. Nitrosopiperidine and nitrosodipropylamine were the most effective inhibitors. Nitrosopyrrolidine and diethylnitrosamine were also effective inhibitors, but nitrosomorpholine was only a weak inhibitor. Nitrosoproline, a noncarcinogenic nitrosamine, also inhibited DMN demethylase, but it exhibited a biphasic inhibition profile. Secondary amines corresponding to the nitrosamines studied inhibited DMN demethylase in a manner similar to the nitrosamines and in the same quantitative range. The similarity of the inhibition with the nitrosamines and the amines suggests that interaction of nitrosamines with DMN demethylase is largely determined by structural characteristics of the amine moiety. (8 refs)

- 79-0194 Formation and Loss of Alkylated Purines from DNA of Hamster Liver after Administration of Dimethylnitrosamine.** (Eng) Stumpf, R. (Dept. Physiology, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033); Margison, G. P.; Montesano, R.; Pegg, A. E. *Cancer Res* 39(1): 50-54; 1979.

The methylation of hamster liver DNA was studied as a function of dose of dimethylnitrosamine (DMN). 7-Methylguanine levels were proportional to DMN doses over the range 10 μ g/kg to 25 mg/kg when measured 5-24 hr after treatment. This product was lost from the DNA at a rate greater than expected from spontaneous depurination at neutral pH, suggesting that enzyme-catalyzed excision takes place. O⁶-Methylguanine (OMG) levels were not proportional to

doses over this range but were much lower than expected (based on 7-methylguanine levels) when measured 5-24 hr after DMN doses below 0.5 mg/kg. This result may be due to the presence of an enzyme capable of removing OMG from DNA efficiently, provided the methylation level is low. The presence of such an enzyme in hamster liver extracts was demonstrated by incubation of the extracts with methylated DNA. The extracts significantly decreased the content of OMG in acid-precipitable DNA. However, when DMN doses above 0.5 mg/kg were used, removal of OMG occurred much more slowly, and the capacity of hamster liver to carry out removal of OMG from DNA in vivo was considerably lower than that of rat liver. The possible relevance of these findings to the relative susceptibility of these species to liver cancer induction by single doses of DMN is discussed. (20 refs)

- 79-0195 On Determination of Safe Concentrations of Carcinogenic N-Nitrosamines in Water.** (Rus) Basieva, T. Kh. (Cancer Res. Center, Moscow, USSR); Mikhailovskii, N. Ia.; Il'nitskii, A. P.; Korolev, A. A. *Gig Sanit* (10): 28-34; 1978.

Based on the literature data concerning the carcinogenicity of N-nitrosamines for rats, an attempt was made to calculate the permissible concentration of N-diethylnitrosamine (DENA) in water. Computer analysis of the results of experiments on the carcinogenicity of po administration of DENA to rats showed that a daily dose of 0.007 mg/kg did not induce tumors. Extrapolation of these findings to humans shows that the maximal permissible dose would be 10 mg/kg/d (0.03 µg/liter/d). (11 refs)

- 79-0196 Temperature Effects During and After the Diethylnitrosamine Treatment on Liver Tumorigenesis in the Fish, *Oryzias latipes*.** (Eng) Kyono, Y. (Zoological Inst., Faculty Science, Univ. Tokyo, Tokyo 113, Japan). *Eur J Cancer* 14(10): 1093-1097; 1978.

Four groups of medaka (*Oryzias latipes*) were treated with diethylnitrosamine (DENA: 100 ppm in drinking water) for 8 wk. Two groups were kept at a high temperature (22-25°C) and two at a low temperature (5-6°C). After DENA treatment, one of the high-temperature groups was transferred to high-temperature normal tap water (H.H group) and another to low-temperature tap water (H.L group). L.H and L.L groups were derived similarly. At 8 and 12 wk after the beginning of the experiment, about 10 fish in each group were sacrificed for histological observation. Many tumor nodules were found in the livers of fish in the H.H and H.L groups, but the number and the size of the nodules were greater in the H.H group than in the H.L group. In contrast, no tumor nodules were observed in L.H and L.L groups that were treated with DENA at a low temperature. These results suggest

an appropriately high temperature is necessary for the formation and the growth of tumor nodules. (16 refs)

- 79-0197 Phospholipids of the Endoplasmic Reticulum Membranes in Normal Rat Liver and During Early Stages of Carcinogenesis.** (Rus) Berdinskikh, N. K. (Inst. Problem Oncology, Kiev, USSR); Sanina, O. L.; Mel'nikova, N. N. *Vopr Onkol* 24(10): 42-48; 1978.

The phospholipid content of endoplasmic reticulum of rat liver was examined in random-bred albino rats: group 1 received diethylnitrosamine (DENA; 0.06% in drinking water), group 2 received a noncarcinogenic analog of DENA, diethylamine (DEA; dose as before), and group 3 served as control. Within 1-4 wk of the initiation of the experiment, rats were sacrificed and the content of phospholipids in the membranes of the liver endoplasmic reticulum was assessed by thin layer chromatography. DENA-induced changes in the phospholipid content were detected in both fractions of the endoplasmic reticulum: the total phospholipid content in the granular reticulum showed a 2.5-fold decrease during the 1st wk, while the agranular reticulum showed a 75% increase in phospholipid content during the 3rd wk of the experiment. The phospholipid content in rats treated with DEA did not differ significantly from controls. (12 refs)

- 79-0198 Epithelial Differentiation of the Embryonic Hamster Trachea and Its Significance for Studies on Diethylnitrosamine Transplacental Carcinogenesis.** (Eng) Emura, M. (Lab. Cell Biology, Aichi Cancer Center Res. Inst., Nagoya 464, Japan); Mohr, U. In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 1015-1031; 1977.

To investigate whether the susceptibility of cells to diethylnitrosamine is correlated to a certain differentiated state of the prenatal tracheal epithelia, Syrian golden hamsters received a single sc injection of 45 mg diethylnitrosamine (DEN)/kg on one of the 15 days of pregnancy. Fifteen groups of six pregnant females were treated; mothers and weaned offspring were observed until spontaneous death, necropsied, and examined histologically. Respiratory tumors were evident in offspring of animals treated on the last 4 days of gestation, reaching an incidence of 95% on day 15 (19/20 animals). Tumors in the larynx and trachea (squamous cell papillomas and papillary polyps) were most common, and tracheal tumors increased particularly the later the carcinogen was administered. Several adenocarcinomas and one squamous cell carcinoma of the nasal cavities and several pulmonary bronchiogenic adenomas were also found in the offspring. A high incidence of respiratory tract tumors also occurred in the

mothers. Histological examination of tracheal epithelium of fetal hamsters from untreated mothers revealed that this epithelium is composed of one layer of columnar cells until day 12 of gestation and then differentiates into luminal, basal, and mucous progenitor cells. Whereas chromatin was homogeneously dispersed in early development, on day 12 it began a progressive condensation. The total volume and functional competence of the endoplasmic reticulum increased during this time. The mitotic activity of the tracheal epithelia was inversely related to the incidence of tracheal tumors and the degree of epithelial differentiation. The results demonstrate a positive correlation between the ultrastructural features of developing tracheal epithelia and their biochemical capacity to metabolize DEN. (18 refs)

79-0199 Definition of Stages During Hepatocarcinogenesis in the Rat: Potential Application to the Evaluation of Initiating and Promoting Agents in the Environment. (Eng) Sirica, A. E. (McArdle Lab. Cancer Res., Medical Sch., Univ. Wisconsin, Madison, WI); Barsness, L.; Goldsworthy, T.; Pitot, H. C. *J Environ Pathol Toxicol* 2(1): 21-28; 1978.

Agents that initiate and promote rat hepatocarcinogenesis were evaluated by giving female Sprague-Dawley rats a single intragastric instillation of diethylnitrosamine (DEN; 10 mg/kg) 24 hr after partial hepatectomy (67%); 2 mo later, 0.05% phenobarbital feeding was started in some of the animals and continued for 6 mo. In animals treated with DEN + PB, the number of liver foci exhibiting an altered enzyme histochemistry was increased at least fivefold over those produced in liver by DEN alone. Seven of eight DEN + PB-treated rats developed hepatocellular carcinomas, whereas no such neoplasms were seen in animals treated with DEN alone. None of the five animals that received PB alone showed enzyme-altered foci or neoplastic lesions in their livers. Three enzyme markers (glucose-6-phosphatase, canalicular ATPase, and γ -glutamyl transpeptidase) were used to evaluate the phenotypes of the enzyme-altered foci. Seven phenotypes were delineated in livers of both the DEN-treated group and the group treated with DEN + PB, but the quantitative pattern of phenotypic heterogeneity was different in the two groups. These results support the existence of a two-stage mechanism of liver carcinogenesis and suggest an in vivo screening model that appears capable of distinguishing between initiating and promoting agents in hepatocarcinogenesis. (30 refs)

79-0200 Topical Nitrogen Mustard Induced Carcinogenesis. (Eng) Kravitz, P. H. (Sub-Section Dermatology, Brown Univ., Providence, RI, 02908); McDonald, C. J. *Acta Derm Venereol (Stockh)* 58(5): 421-425; 1978.

Two cases of mycosis fungoides (MF) complicated by the development of cutaneous squamous cell carcinomas (SCC)

following nitrogen mustard (NM) therapy are reported. A 64-yr-old woman with MF of 20 yr duration had applied topical NM (10 mg of powder diluted in 20 ml water and 20 ml propylene glycol) to her entire body, including her face, for an 8-hr period daily. After 7 yr, she developed a superficially invasive SCC of the anterior chest and invasive SCC of her cheeks. Prior to NM, she had been treated with electron beam therapy and systemic chemotherapeutic agents. The second patient, an 82-yr-old man with MF of 40 yr duration had applied NM daily for 3 hr when an infiltrating SCC on the left lower leg was discovered. He also had been treated previously with various chemotherapeutic agents. The carcinoma was treated with x-radiation. Subsequently, recurrent tumors developed at the original tumor site, left proximal thigh, and upper back. Long-term application of topical NM to the skin probably rendered both patients susceptible to the development of multiple SCC. However, the previous or cumulative effects of systemic chemotherapy cannot be discounted. The patients did not have clinical evidence of chronic solar damage at their tumor sites. The virulence of the SCC in the man may have been related to external stimuli (radiation) or to impaired delayed hypersensitivity. (17 refs)

79-0201 Volatile Nitrosamines in Normal Human Faeces. (Eng) Wang, T. (Ontario Cancer Inst., 500 Sherbourne St., Toronto, Ontario, Canada M4X 1K9); Kakizoe, T.; Dion, P.; Furrer R.; Varghese, A. J.; Bruce, W. R. *Nature* 276(5685): 280-281; 1978.

The presence of volatile nitrosamines in normal human feces was studied by gas-liquid chromatography and high-pressure liquid chromatography. Freeze-dried condensates of fecal samples showed several peaks attributed to nitroso compounds, the five major compounds being N-nitrosodimethylamine (NDMA: amount present in typical condensate, 0.04 $\mu\text{g/liter}$), N-nitrosodiethylamine (NDEA, 0.10 $\mu\text{g/liter}$), N-nitrosodibutylamine (NDBA, 0.08 $\mu\text{g/liter}$), N-nitrosopiperidine (NPPI, 0.08 $\mu\text{g/liter}$), and N-nitrosomorpholine (NMOR, 0.02 $\mu\text{g/liter}$). In addition, fecal samples were collected from 12 healthy volunteers, immediately extracted with dichloromethane, and analyzed chromatographically. NDMA (0.3-1.5 $\mu\text{g/kg}$) was found in 11 samples, NDEA (0.2-13 $\mu\text{g/kg}$) in 8 samples, NDBA (< 1 $\mu\text{g/kg}$) in 2 samples, and NPPI and NMOR (< 2 $\mu\text{g/kg}$) in 3 and 5 samples, respectively. Many levels were higher than those found in the freeze-dried condensates, presumably as a result of losses of the volatile compounds during freeze-drying. The source of the nitroso compounds in the feces has not been established, but it is likely that they are produced in the lower gastrointestinal tract. (26 refs)

79-0202 Differential Mutagenicity of N-Methyl-N-nitrosocarbamate Insecticides in *Escherichia coli* Strains Having Different DNA Repair Capacities. (Eng) Yoshikawa, K. (Dept. Microbiology, Natl. Inst. Hygienic

Sciences, Kamiyoga 1-18-1, Setagaya-ku, Tokyo, Japan); Uchino, H.; Kurata, H. *Mutat Res* 54(3): 283-288; 1978.

The lethal and mutagenic effects of 1-naphthyl N-methyl-N-nitrosocarbamate (NAC), 3-methylphenyl N-methyl-N-nitrosocarbamate (MTMC), and 3,4-dimethylphenyl N-methyl-N-nitrosocarbamate (MPMC) on four isogenic strains of *Escherichia coli* having the same auxotrophic marker (arg⁻ Fam) were studied. Strains R15 (defective in the DNA polymerase I) and NG30 (recombination deficient) were more sensitive to killing by NAC, MTMC, and MPMC than were strains H/r30R (wild-type) and Hs30R (excisionless). Strains R15, H/r30R, and Hs30R showed similar susceptibility to the mutagenic effects of NAC, MTMC, and MPMC and were 10-fold more sensitive to the mutagenic effects of MTMC and 20-fold more sensitive to the mutagenic effects of MPMC than was strain NG30. NAC was not significantly mutagenic for NG30. The data suggest that the mutagenic effects of MTMC and MPMC are similar to that of N-methyl-N'-nitro-N-nitrosoguanidine, whereas that of NAC is similar to those of methyl methane-sulfonate or x-rays. The major damage to DNA by the three insecticides was not excisable by uvrA⁺-dependent excision repair and was probably methylation on the DNA. (7 refs)

79-0203 Reduced Carcinogenicity of Urethane for Thymusless Mice Compared with Their Immunologically Normal Siblings. (Rus) Kaledin, V. I. (Lab. Cancer Genetics, Inst. Cytology, Genetics, Novosibirsk, USSR); Gruntenko, E. V.; Morozkova, T. S. *Biull Eksp Biol Med* 86(11): 574-576; 1978.

The model of urethane carcinogenesis in athymic nude (nu/nu) mice was used for verification of Burnet's hypothesis on the role of immunological surveillance in oncogenesis. The progeny of the mating +/nu x +/nu (1/4 of which were nu/nu and 3/4 of which were phenotypically and immunologically normal) were inoculated ip with urethane (two 1-mg/g doses at a 7-day interval). The mice were paired (1 nude and 1 normal), and pairs were followed until the death of one of the partners, after which the second was sacrificed and the number of lung adenomas in the animals was compared. Of 10 immunologically normal mice, 7 were found to have lung adenomas, compared with 2/10 nude mice. The av number of adenomas per mouse was also significantly greater in normal mice than in their athymic siblings (1.2 and 0.2, respectively). (11 refs)

79-0204 Myelomatosis After Phenytoin Therapy. A Chance Association? (Eng) Matzner, Y. (Dept. Hematology, Hadassah Univ. Hosp., Jerusalem, Israel); Polliack, A. *Scand J Haematol* 21(4): 309-312; 1978.

The case report is presented of a 54-yr-old patient who developed monoclonal gammopathy followed by IgG-lambda

multiple myeloma during chronic (20-yr) diphenylhydantoin (phenytoin; Dilantin) therapy for epilepsy. The patient also suffered from diabetes mellitus and hypertension. He did not develop the signs of hypersensitivity to phenytoin or the lymphadenopathy during the 20 yr of continuous therapy prior to the development of the monoclonal gammopathy. The monoclonal gammopathy was found by chance, but within 8 mo classical multiple myeloma of IgG-lambda type had developed. Despite the known association between phenytoin and the development of immunosuppression and lymphoma, this case is regarded as a probable coincidence. Nevertheless, it is recommended that phenytoin-treated patients be examined regularly for lymphadenopathy and monoclonal gammopathy. (27 refs)

79-0205 Effect of 1,3-Bis(2-chloroethyl)-1-nitrosourea on *Escherichia coli* DNA Repair System. (Eng) Tashima, M. (First. Div. Internal Medicine, Faculty Medicine, Kyoto Univ., 53 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606, Japan); Sawada, H.; Uchino, H.; Nishioka, H. *Gann* 69(5): 695-698; 1978.

The antibacterial effect of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) on isogenic strains of *Escherichia coli* with normal or defective DNA repair systems was studied. Growth of strains lacking the *rec-A* gene was inhibited by BCNU at much lower concentration than in the case of those possessing it. This result suggests that BCNU-induced DNA damage in *E. coli* is effectively repaired by postreplication repair. (16 refs)

79-0206 Reaction of DNA with Alkylating Agents. Quantitation of Alkylation by Ethylnitrosourea of Oxygen and Nitrogen Sites on Poly[dA-dT] Including Phosphotriester Formation. (Eng) Jensen, D. E. (Fels Res. Inst., Temple Univ. Health Sciences Center, Philadelphia, PA, 19140); Reed, D. J. *Biochemistry* 17(24): 5098-5107; 1978.

The alkylation of oxygen and nitrogen sites on poly[dA-dT] by ethylnitrosourea (ENU) was studied by anion-exchange high-pressure liquid chromatography. The degree of phosphate group ethylation was 60% to 65% of the total assayed alkylation under a variety of reaction conditions. The phosphate reaction appeared to be independent of nucleotide base sequence. There was some reaction preference for one of the available oxygen sites in the phosphate group relative to the other, as determined by the resolution of ethyl dideoxynucleoside phosphotriester diastereomers. Some properties of these phosphotriester diastereomers are described. Quantitation of base alkylation showed a very high level of ethylation at the 2-position oxygen on the thymine moiety (approx 30% of the total alkylation). A low degree of ethylation occurred at the 4-position oxygen site on thymine and the 3-position nitrogen on adenine (3%-5% of the total ethylation pro-

ducts). Addition of sodium ion, tetramethylammonium ion, or magnesium ion to the poly[dA-dT]-ENU mixture resulted in a general decrease in total alkylation. The latter two ions decreased the base alkylation to phosphate alkylation ratio, whereas sodium ion had little effect. (37 refs)

79-0207 Reaction of DNA with Alkylating Agents. Differential Alkylation of Poly[dA-dT] by Methyl-nitrosourea and Ethylnitrosourea. (Eng) Jensen, D. E. (Fels Res. Inst., Temple Univ. Health Sciences Center, Philadelphia, PA, 19140). *Biochemistry* 17(24): 5108-5113; 1978.

The methylation of poly[dA-dT] resulting from incubation with methylnitrosourea (MNU) or ethylnitrosourea (ENU) was studied. Modification of the phosphate-group oxygen atoms using MNU accounted for 65%-75% of the total asayed alkylation under a variety of reaction conditions. Some reaction preference for one of the available nucleotide phosphate oxygen sites relative to the other was indicated, as determined by the differential yield of methyl dideoxynucleoside phosphotriester diastereomers. Methylation at the 3-position nitrogen atom on the adenine moiety amounted to approx 25% of the total alkylation. O²-thymine modification accounted for only 3%-5% of the total methylation products. MNU was approx twofold more effective than ENU with regard to total poly[dA-dT] alkylation. In contrast, ENU was much more effective at O²-thymidine alkylation, with this modification accounting for 40%-50% of the total methylation products. However, ENU alkylation of the 3-position nitrogen in deoxyadenosine was <10%. A reaction mechanism to account for these differences is discussed. (16 refs)

79-0208 Interaction of 1,1'-Ethylene-bis(1-nitrosourea) with Nucleic Acids and Proteins In Vitro. (Eng) Morimoto, K. (Dept. Medical Chemistry, Natl. Inst. Hygienic Sciences, Kamiyoga 1-18-1, Tokyo, Japan); Yamahara, T.; Miyahara, M.; Nakadate, M.; Suzuki, I. *Gann* 69(5): 649-655; 1978.

The binding of radioactivity from 1,1'-ethylenebis(1-nitrosourea) (EBNU) labeled with ¹⁴C in the carbonyl or ethylene residue to nucleic acids, proteins, and synthetic biopolymers was investigated in vitro. EBNU [carbonyl-¹⁴C] (9.5 μCi/mg) and EBNU [ethylene-¹⁴C] (8.1 μCi/mg) were incubated with a suspension of L1210 cells at 37 C, and binding of radioactivity was measured. The initial binding rate of both labeled compounds to the acid-insoluble fraction of the whole cells was the same for 30 min, after which the binding of radioactivity from EBNU [ethylene-¹⁴C] reached a max and that from EBNU [carbonyl-¹⁴C] continued to increase proportionally with time up to 3 hr. EBNU [carbonyl-¹⁴C] was bound to cytoplasmic and nuclear proteins but not to nucleic acids in L1210 cells, but that from EBNU [ethylene-¹⁴C] was bound to both proteins and nucleic acids. These findings were confirmed in model experiments in which puri-

fied nucleic acids, proteins, and synthetic biopolymers were used. The preferential binding of both labeled compounds to polylysine and polyhistidine as well as the selective binding of EBNU [ethylene-¹⁴C] to polyarginine might be responsible for the chemical and biological modification of basic proteins in chromatin by EBNU. (17 refs)

79-0209 Herbicidal Phenylalkylureas as Possible Mutagens: I. Mutagenicity Tests with Some Urea Herbicides. (Eng) Seiler, J. P. (Swiss Federal Res. Station, CH-8820 Waedenswil, Switzerland). *Mutat Res* 59(2/3): 353-359; 1978.

The mutagenic properties of 10 phenylalkylureas were tested in three different mutagenicity assays: (1) inhibition of testicular DNA synthesis (DSI), (2) the induction of point mutations in *Salmonella typhimurium* strain TA1535, and (3) chromosome damage assessed by the micronucleus test. Nine of the ten compounds gave positive results in the DSI test: N-methyl-N'-phenylurea, N,N-dimethyl-N'-phenylurea (fenuron), N,N-dimethyl-N'-(3-chlorophenyl)-urea, N,N-dimethyl-N'-(4-chlorophenyl)-urea monuron, N,N-dimethyl-N'-(3,4-dichlorophenyl)-urea (diuron), N,N-dimethyl-N'-(3-chloro-4-methylphenyl)-urea (chlorotoluron), N,N-dimethyl-N'-(3-chloro-4-methoxyphenyl)-urea (metoxuron), N,N-dimethyl-N'-(3-trifluoromethylphenyl)-methoxyphenyl)-urea (fluometuron), and N-methoxy-N-methyl-N'-(3,4-dichlorophenyl)-urea (linuron). Six of these nine compounds were weakly mutagenic in the *S. typhimurium* test. These compounds had a marginal effect on mammalian chromosomes, as evidenced by the very weak responses in the micronucleus test. The compound yielding negative results in all tests was N-methoxy-N-methyl-N'-(4-chlorophenyl)-urea (monolinuron). Since one member of this group of chemicals, monuron, is a recognized carcinogen, the results of the DSI assay indicate that a more thorough investigation of the mutagenic potential of these herbicides is needed. (16 refs)

79-0210 The Rate of Hydrolysis of Methyl Phosphotriesters in DNA under Conditions Used in Alkaline Sucrose Gradients. (Eng) Shooter, K. V. (Carcinogenesis Div. Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks HP8 4SP, England); Merrifield, R. K. *Biochim Biophys Acta* 521(1): 155-159; 1978.

The relationship between the frequency of chain breaks in alkaline sucrose gradients and the concentration of phosphotriesters (PTE's) in DNA was investigated. Methyl PTE's were introduced into phage T7 DNA by incubating the latter with 0.08 mg/ml N-methyl-N-nitrosourea at 37 C for 30 min. The rate of PTE degradation in 0.3 M NaOH/0.7 M NaCl was determined by measuring the mean sedimentation rate of the DNA using boundary velocity ultracentrifugation. Hydrolysis of the methyl PTE's was complete after 15 hr at 20

C and after 2-3 hr at 37 C. The number of breaks/single strand of phage T7 DNA due to the PTE's alone was 11.7 at 20 C and 13.2 at 37 C, but continuous background degradation of DNA introduced an extra 3-4 breaks/molecule at 20 C and approx 6 breaks/molecule at 37 C. Therefore, the background rate was 6.3 and 63.0 breaks/10⁶ nucleotides/hr at the two temperatures, respectively. Incubation for 1 hr at 37 C would introduce breaks equivalent to the number produced by complete hydrolysis of the PTE's present and would probably lead to a best estimate of the concentration of these lesions. The background degradation rate would have to be considered in assessing the accuracy of the estimate. The nature of the alkyl group in the PTE may affect the hydrolysis rate in alkali and the fraction of the lesions that, on hydrolysis, lead to chain breaks rather than to simple loss of the alkyl group. (12 refs)

- 79-0211 A New Animal Model for the Direct Induction of Neoplasms During Embryonic and Fetal Development.** (Eng) Jurgelski, W. (Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC); Hudson, P. M.; Dunn, R. L.; Falk, H. L. In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 1033-1059; 1977.

Neoplasms induced postnatally with ethylnitrosourea (ENU) in the opossum were studied to demonstrate the potential of the opossum as a model for carcinogenesis. In two experiments, 532 opossums were divided by litter into 10 groups according to age (< 1 day, and 1, 2, 3, 4, 6, 8, 10, 12, and 16 wk). In the first experiment, animals were given approx 100 mg/kg ENU as a single po dose. In the second experiment, the same total dose was administered po in increments of 25 mg/kg given every other day. One or two animals in each litter served as controls. The animals developed a spectrum of mesenchymal and epithelial embryonal and 'adult type' neoplasms with diverse latencies and a range of malignancies comprising 43 different tumors distributed among 21 different sites. Several of the tumors previously had not been induced in laboratory species by systemic administration of a carcinogen. Fifty-four percent had one or more primary neoplasms; 73% of the tumor bearers had more than one primary. Thus, the opossum early in postnatal life is a useful model for the induction and characterization of certain of the major dysontogenetic neoplasms that have been difficult or impossible to reproduce in traditional laboratory species. The opossum also appears to have potential as a model for several tumors of adult life, particularly for malignant neoplasms of the lung, liver, intestine, and skin and, possibly, of the pancreas and prostate. It may be of special value in experimental perinatal carcinogenesis under conditions in which extrafetal activation or inactivation or a short biological half-life of the carcinogen may obscure or prevent the response of the target organ. (53 refs)

- 79-0212 Notes on the Influence of N-Phenyl-N'-methylurea on Growth of B-77 Tumors in Rats.** (Slo) Paulov, S. (Univerzita Komenskeho, Bratislava, Czechoslovakia); Novotna, L. *Biologia* 33(8): 677-679; 1978.

The effect of N-phenyl-N'-methylurea (PMU; 0.025-2.500 µg/animal ip) on the growth of sc transplanted B-77 tumors (derived from LW embryonic fibroblasts transformed by B-77 avian sarcoma virus) was studied in six inbred Lewis LW rats weighing 180 g. PMU, administered 1 wk after tumor transplantation, markedly stimulated tumor growth, compared with that in two control animals not treated with PMU. The growth-stimulating effect was highest in the dose range 1-3 µg/animal, which caused a fivefold increase in tumor size, compared with the controls. A twofold increase in tumor size was induced by doses of 0.01-100 µg/animal. (5 refs)

- 79-0213 Changes in Surface Morphology Associated with Ethylnitrosourea-induced Malignant Transformation of Cultured Rat Brain Cells Studied by Scanning Electron Microscopy.** (Eng) Winslow, D. P. (Dept. Cell Pathology, Sch. Pathology Middlesex Hosp. Medical Sch., Riding House St., London W1P 7LD, England); Roscoe, J. P.; Rowles, P. M. *Br J Exp Pathol* 59: 530-539; 1978.

Cultures of cells clonally derived from either normal adult rat brain (ARBO) or a culture of a mixed glioma induced by ethylnitrosourea (ENU) were studied by scanning electron microscopy. ARBOC9 and ARBOC11 cultures, malignant glioma cultures A15A5 and A15A10, and rat brain cell clones (38D, 38E, 38F, 38G, 40D, and 40E) from rats transplacentally exposed to 40 mg/kg ENU were examined. Clones C9 and C11 were both extremely flat with few surface features; in particular, C11 cells were almost devoid of microvilli and had few intercellular filopodia. Cell boundaries were indistinct due to the very close contact between the cells. A15A5 and A15A10 clones, however, both consisted of extremely condensed bipolar cells, spherical cells, and pyramidal cells. Cell-cell and cell-surface contact was limited. Cell surfaces had long filopodia, some ruffles, and numerous blebs. The 38D, 38E, and 40D cultures were tumorigenic at the earliest times tested (30-33rd passage), and these cells appeared generally similar to A15A5 and A15A10 cell lines with many blebs, pleomorphic microvilli, and long filopodia, although these changes were less frequently seen in line 40D. The other brain cell cultures were not tumorigenic at the time of first testing and were composed mostly of flat cells with few surface features. Line 38F became tumorigenic at the 48th transfer, and at about this time it also began to demonstrate high surface activity. These results indicate that observed differences in cell surface activity represent a distinction between malignant and normal brain cells in culture. (20 refs)

- 79-0214 Toxicity of Ethylenethiourea in Pregnant Cats.** (Eng) Khera, K. S. (Bureau Chemical Safety, New Res. Center, Natl. Health and Welfare, Ottawa, Ontario, Canada K1A 0L2); Iverson, F. *Teratology* 18(3): 311-313; 1978.

To test the teratogenicity of ethylenethiourea (ETU) in cats, time-mated adult cats were given 5, 10, 30, or 60 mg/kg ETU po during days 16 to 35 of gestation or 120 mg/kg po from day 16 of gestation until signs of intoxication became evident (between days 27 and 34 of gestation). Cats given more than 5 mg/kg/day ETU showed toxicity of delayed onset characterized by wt loss, ataxia, tremors, and hind-limb paralysis. Four cats in the 30 mg/kg group, two in the 60 mg/kg group, and five in the 120 mg/kg group died or were killed in a moribund condition. Abortions occurred in all, including the untreated control groups and were unrelated to treatment. Nonpregnant cats were also found in all groups, the number being unrelated to treatment. Eleven of 35 live fetuses obtained from the moribund cats were malformed (coloboma, umbilical hernia, cleft palate, and/or spina bifida). Fetuses obtained from cats that remained healthy or outlived toxicosis showed no ETU-related effects on viability or wt. The data in general showed no clear evidence for teratogenicity of ETU in live fetuses. (7 refs)

- 79-0215 Determination of a Non-volatile N-Nitrosamine on a Food Matrix.** (Eng) Walters, C. L. (British Food Manufacturing Industries Res. Association, Randalls Rd., Leatherhead, Surrey, KT22 7RY, England); Downes, M. J.; Edwards, M. W.; Smith, P. L. *Analyst* 103(1232): 1127-1133; 1978.

A method devised for the determination of N-nitrososarcosine in soln, in which the N-nitrosamine in soln is denitrosated with hydrogen bromide to form volatile products that are rapidly removed and analyzed in a chemiluminescence analyzer, was extended to the determination of N-nitrososarcosine on a food matrix (powdered corn flakes). This procedure was carried out to determine whether the release of nitrogen oxide using hydrogen bromide is impaired in this situation. Nine 10-g samples of powdered corn flakes, each with 22 µg of added N-nitrososarcosine, were analyzed. The results obtained were in the range 15.4-19.3 µg, the mean value being 17.52 ± 1.53 µg. This method was less sensitive when used for N-nitrososarcosine determination in the food matrix than when used for determination in simple soln. Differentiation of N-nitrososarcosine and a number of other N-nitrosamines from inorganic nitrite was achieved by decomposing the nitrite with acetic acid prior to the denitrosation of the N-nitroso compounds. The other N-nitrosamines gave volatile products following denitrosation with hydrogen bromide that were detectable using a chemiluminescence analyzer; this was also true of the nitrosamides N-nitroso-N-methylurea, N-nitroso-N-ethylurea, and N-nitroso-N-methylurethane. Further, the procedure developed for the differentiation of N-nitrososarcosine and nitrite

was successfully extended to these N-nitrosamines and N-nitrosamides. The small amount of nitrosation of the secondary amines during the differentiation process was prevented by the addition of ascorbyl palmitate. In differentiating between large amounts of nitrite and much lower levels of N-nitroso-sarcosine on corn flakes, using a chemiluminescence analyzer, the duration of the response from the nitrite could be shortened by freeze-drying the food matrix in the presence of ascorbic acid. (13 refs)

- 79-0216 Analysis of Synthetic RNA-directed DNA Polymerase Activities in the Spleen of a Rat with Myelogenous Leukemia Induced by N-Nitroso-N-butylurea.** (Eng) Kozu, T. (Div. Serology and Virology, Saitama Cancer Center Res. Inst., Inamachi, Kitaadachi-gun, Saitama-ken 362, Japan); Aida, M.; Ikawa, Y.; Seno, T. *Eur J Cancer* 14(10): 1065-1076; 1978.

DNA polymerase activities from the spleen of a Sprague-Dawley rat with myelogenous leukemia induced by N-nitroso-N-butylurea were examined with respect to their possible association with RNA tumor viruses. Phosphocellulose chromatography of the extract from the leukemic spleen gave a single peak of poly(rA)-(dT)12-18-directed activity that coincided with that of DNA polymerase γ obtained from normal rat spleen, whereas chromatography of the extract from virus-producing cultured R35 rat mammary tumor cells or from the viruses themselves gave a unique peak of activity different from that of DNA polymerase γ . These viruses appeared to be one of the rat endogenous viruses similar to R35 virus. The peak from the leukemic spleen showed several enzymatic properties similar to those of DNA polymerase γ obtained from normal rat spleen, but different from those of the R35 viral DNA polymerase. The peak from the leukemic spleen responded to poly(rCm)-(dG)12-18, which is reported to be specific for viral reverse transcriptase. However, the DNA polymerase γ fraction from normal rat spleen also responded to the template primer to the same degree. Postmitochondrial fractions from the leukemic spleen gave poly(rA)-(dT)12-18-directed activity that sedimented at a density of 1.17 g/cm³ on sucrose. Addition of a nonionic detergent was not required for the activity. For the R35-like viruses, which banded at a density of 1.16 g/cm³, detergent was required to detect the activity. The results demonstrated that any unique DNA polymerase activity different from cellular DNA polymerase γ was not detectable from the spleen of a leukemic rat, under conditions in which reverse transcriptase activity was detectable in the virus-producing control rat cells. (33 refs)

- 79-0217 Mutagenicity of 4-Nitropyridine-1-oxide for *Salmonella typhimurium*.** (Eng) Auletta, A. E. (JRB Assoc., Inc., McLean, VA, 22101); Price, P. J. *Mutat Res* 58(2/3): 371-374; 1978.

4-Nitropyridine-1-oxide (4-NPO) was screened for mutagenic activity in *Salmonella typhimurium* and for its ability to

inhibit repair-deficient strains of this organism. Mutagenicity was determined using *S. typhimurium* strain TA100 in both a spot test and a pour-plate assay. Enzyme activation with liver microsomes was not performed because 4-NPO proved to be a direct-acting mutagen for *S. typhimurium*. In the repair test using strains TA1978 and TA1538 (repair deficient), there was no appreciable difference in the zone of inhibition of either strain with 4-NPO. In previous studies, 4-NPO had preferentially inhibited the growth of *polA*- strains of *Escherichia coli* over the parent wild-type strains but had no differential effect on cell killing between parent and UV-sensitive mutant strains of *B. subtilis* and *S. cerevisiae*. The UV-sensitive strains of *B. subtilis* and *S. cerevisiae* were also insensitive to methyl methanesulfonate and N-methyl-N'-nitro-N-nitrosoguanidine, suggesting a common factor in the repair mechanism for damage due to these agents and to 4-NPO. These results support the use of the Salmonella/microsomal assay as a prescreen for potential carcinogens. The results of the repair test suggest that the *polA*- mutants of *E. coli* are the organisms of choice for use in such an assay system. (8 refs)

79-0218 Survey of Cured Meat Products for Volatile N-Nitrosamines: Comparison of Two Analytical

Methods. (Eng) Havery, D. C. (Div. Chemistry and Physics, Food and Drug Admin., Washington, DC, 20204); Fazio, T.; Howard, J. W. *J Assoc Off Anal Chem* 61(6): 1374-1378; 1978.

Gas chromatography/mass spectrometry and mineral oil distillation-thermal energy analysis were used to analyze 106 cured meat samples for 14 volatile N-nitrosamines. N-Nitrosopyrrolidine (5-75 ppb) was confirmed in fried bacon, and unconfirmed trace levels of N-nitrosodimethylamine were found in other cured meats. There was good agreement between the analytical methods, especially at the 10-ppb level, and excellent agreement between analyses of an identical sample extract. (25 refs)

79-0219 The Oncogenic Implications of Chronobiotics in the Synchronization of Mammalian Circadian

Rhythms: Barbiturates and Methylated Xanthines. (Eng) Ehret, C. F. (Div. Biology and Medical Res., Argonne Natl. Lab., Argonne, IL, 60439); Dobra, K. W. In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 1101-1114; 1977.

This study shows that levels of phenobarbital (PB) in the rat diet at and near those that are cocarcinogenic also induce circadian dyschronism. Male Charles-River rats fed 0.05%-0.3% PB in the diet for 7 days maintained nearly a

constant body temperature, whereas controls maintained a strong circadian rhythm of deep body temperature. Any tendency in the experimental animals toward circadian oscillation became less evident with increasing dosage. Power spectral analysis was used to determine if there was a decrease in the variance of the circadian component of the frequency spectrum and to determine if the transient frequencies were randomly distributed or if a dominant frequency with a < 24-hr period became evident. As the percent of PB in the diet increased, the variance of the 24-hr component diminished, and there was no significant increase in any other component of the frequency spectrum. Previous epidemiological evidence shows that persons at high risk of cancer include those who have had genetic deficiency diseases or who have taken drugs that interfere with the putative molecular-genetic pathways for circadian regulation, especially those interfering with the storage and regulation of energy reserves and the regulation of the catecholamine and indoleamine synthetic pathways. It is suggested that each time that the circadian biological oscillator in a cell is reset by a chronobiotic, there is increased risk of oncogenic damage to the gene-action machinery of the cell; for this reason, all chronobiotics may be oncogenic when taken at a vulnerable phase of the circadian cycle. (42 refs)

79-0220 Reproduction of Major Reactions of Aromatic Carcinogens with Guanosine, Using

HMO-based Polyelectronic Perturbation Theory. (Eng) Scribner, J. D. (Pacific Northwest Res. Foundation, 1102 Columbia St., Seattle, WA, 98104); Fisk, S. R. *Tetrahedron Lett* (48): 4759-4762; 1978.

Three different reactions with guanosine were correctly identified among five aromatic carcinogens, four aromatic amine derivatives and one polycyclic aromatic hydrocarbon derivative, using a simple calculation method. The method is based on the Huckel molecular orbital-based polyelectronic perturbation theory. According to this theory, the likelihood of a bond forming between an atom of a nucleophile and an atom of an electrophile depends on the perturbation energy that develops as these atoms approach each other. (9 refs)

79-0221 Chlorhexidine-induced Lingual Keratosis and Dysplasia in Rats. (Eng) Sonis, S. T. (Sidney

Farber Cancer Inst., Floor 17, Room 81, 44 Binney St., Boston, MA, 02115); Clark, W. B.; Shklar, G. *J Periodontol* 49(11): 585-591; 1978.

A study was undertaken to investigate the effect of chlorhexidine (CHD) ingestion on the tongue mucosa of Lewis rats. Forty-five animals were divided into six groups, the first of which comprised untreated controls (I). Other animals received 0.2% CHD in drinking water for 14 days before sacrifice (II); 0.2% CHD in drinking water for 14 days, then tap water before sacrifice at 30 days (IIa); 0.2% CHD in water for 14 days (III); 0.02% CHD in water for 30 days (IIIa);

and 0.2% CHD in water for 30 days (IV). All tongues were removed at sacrifice for histological examination. At 2 wk, approx 50% of the rats in groups II and IV and 20% of group III developed white plaques on the tongue, often associated with ulcerative changes and loss of papillae. Changes were most marked on the dorsal and lateral surfaces, but the ventral side was also affected. Microscopically, these plaques were identified as extensive keratosis, with accompanying dysplasia. Dysplasia was confirmed by hyperchromicity and enlargement of nuclei, with spindling and separation of cells. In regions of keratosis, the width of the stratum corneum was equal to the remainder of the stratified squamous epithelium, and connective tissue below the epithelium was chronically infiltrated with lymphocytes and histiocytes. These changes were present to a lesser degree in animals treated with 0.02% CHD. After one month, all rats in groups IIa, IIIa, and IV demonstrated varying degrees of a return to a normal state both grossly and microscopically, indicating that the animals had developed a tolerance to CHD toxicity. Further evaluation is needed of the progression and resolution of these pathological changes in response to CHD. (16 refs)

- 79-0222 Bromodeoxyuridine Mutagenesis in Mammalian Cells Is Stimulated by Thymidine and Suppressed by Deoxycytidine.** (Eng) Davidson, R. L. (Div. Human Genetics, Children's Hosp. Medical Center, Boston, MA, 02115); Kaufman, E. R. *Nature* 276(5689): 722-723; 1978.

The effects of deoxycytidine (CdR) and thymidine (TdR) on 5-bromodeoxyuridine (BUdR) mutagenesis were investigated in two pigmented Syrian hamster melanoma cell lines, RPMI 3460 and HAB-2E (derived from RPMI 3460, with all thymine residues in nuclear DNA replaced by bromouracil). In most studies, ouabain resistance (OB-r) was used as the marker for mutagenesis. The addition of 1 μ M CdR to the culture media decreased BUdR mutagenicity; a max decrease was obtained with 10 μ M CdR. Similar results were obtained in the presence of aminopterin, which blocks the conversion of CdR to TdR nucleotides, demonstrating that CdR suppresses BUdR mutagenicity without being converted to TdR nucleotides and without altering the amount of bromouracil in DNA. In the absence of CdR, BUdR mutagenicity occurred when the BUdR concentration exceeded 10 μ M. However, in the presence of CdR, BUdR mutagenicity did not occur until the BUdR concentration exceeded 30 μ M. The addition of 10 μ M TdR to 10 μ M BUdR increased the frequency of mutants while decreasing bromouracil substitution. The addition of 100 μ M TdR resulted in a similar stimulation of mutagenesis, even though the bromouracil substitution dropped to a very low level. Stimulation of mutagenesis by TdR was suppressed by CdR. The results were similar with both cell lines and with the use of OB-r or resistance to 18 μ M 6-thioguanine as a marker for mutagenesis. Interactions involving small molecules may play a central part in BUdR mutagenesis in mammalian cells. (15 refs)

- 79-0223 Synthesis of Mutagenic Principles Isolated from L-Glutamic Acid Pyrolysate.** (Eng) Take-da, K. (Faculty Pharmaceutical Sciences, Univ. Tokyo, Bunkyo-ku, Tokyo, Japan); Shudo, K.; Okamoto, T.; Kosuge, T. *Chem Pharm Bull (Tokyo)* 26(9): 2924-2925; 1978.

The synthesis of two mutagenic components of L-glutamic acid pyrolysate, 2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole and 2-aminodipyrido[1,2-a:3',2'-d]imidazole, from 3-amino-8-methylimidazo[1,2-a]pyridine and 3-aminoimidazo[1,2-a]pyridine, respectively, is described. (7 refs)

- 79-0224 A Simple Plate Test for Screening Colicine-inducing Substances as a Tool for the Detection of Potential Carcinogens.** (Eng) Ben-Gurion, R. (Israel Inst. Biological Res., Ness-Ziona, Israel); *Mutat Res* 54(3): 289-295; 1978.

A simple and rapid plate test for screening substances that induce colicine E2 was studied. Colicinogenic auxotrophic bacteria, together with prototrophic indicator cells, were exposed to various test compounds on synthetic plates containing only small amounts of growth factors necessary for the growth of the tester bacteria. The inducing effect of the test compound could be measured quantitatively and was expressed in this way. All of the carcinogenic substances tested were positive in the induction plate test. A dose-response relationship was demonstrated for daunomycin, mitomycin C, and N-methyl-N'-nitro-N-nitrosoguanidine. Benzo(a)pyrene was inductive only after activation with S-9 mix. Chloramphenicol did not induce colicine, indicating that the test can distinguish between substances affecting DNA (presumably carcinogenic) and those affecting protein synthesis. The test is rapid and suitable for nonsterile material, and there are no complications due to phenocopies. (19 refs)

- 79-0225 Oncogenesis, Mutagenesis, DNA Damage, and Cytotoxicity in Cultured Mammalian Cells Treated with Alkylating Agents.** (Eng) Peterson, A. R. (Univ. Southern California Comprehensive Cancer Center, Cancer Res. Lab., Los Angeles, CA, 90033); Peterson, H.; Heidelberger, C. *Cancer Res* 39(1): 131-138; 1979.

Mutation to 8-azaguanine resistance in Chinese hamster V79 cells, and cytotoxicity and the production and repair of alkali-labile lesions in the DNA of V79 and transformable mouse embryo C3H/10T1/2 fibroblasts were measured after the cells had been treated for 2 hr with the monofunctional alkylating agents N-methyl- and N-ethyl-N'-nitro-N-nitrosoguanidine (MNNG and ENNG) and methyl and ethyl methanesulfonate (MMS and EMS). In both cell lines, methylating agents were more cytotoxic than equimolar concentrations of ethylating agents, and MNNG and ENNG were more cytotoxic than MMS and EMS. At equitoxic concentra-

tions, MNNG was 14 times as mutagenic as MMS and it produced 400 times as many alkali-labile lesions; ENNG and EMS produced similar numbers of alkali-labile lesions and were equally mutagenic. A plot of alkali-labile lesions vs mutations was a straight line, but the frequency of alkali-labile lesions was seven orders of magnitude greater than the frequency of mutations; the rate of repair of the alkali-labile lesions varied inversely as the first power of the number of lesions. These findings suggest that mutagenic and alkali-labile lesions are associated but not identical and that neither lesion is associated with cytotoxicity. The results are discussed in the light of chemical theories of alkylation and mutagenesis and are compared with previous studies that show that oncogenic and alkali-labile lesions are not uniformly associated. (33 refs)

- 79-0226 DNA Synthesis Inhibition in HeLa Cells as a Simple Test for Agents That Damage Human DNA.** (Eng) Painter, R. B. (Lab. Radiobiology, Univ. California, San Francisco, CA, 94143). *J Environ Pathol Toxicol* 2(1): 65-78; 1978.

Inhibition of HeLa cell DNA synthesis by DNA-damaging agents was investigated as a test for mutagenic carcinogens. Tests with 17 known carcinogens and/or mutagens showed a positive correlation between DNA synthesis inhibition and potential mutagenicity and/or carcinogenicity. The effect of two DNA-damaging agents administered simultaneously was examined. With UV light and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), the effects were partly additive, but with MNNG and ICR-170 they were not. When UV light was administered simultaneously with hydroxyurea (HU), a non-DNA-damaging inhibitor of DNA synthesis, the UV effects were still evident after HU was removed and the HU-induced DNA synthesis inhibition was reversed. The inhibition of DNA synthesis by ICR-170 and by MNNG was less in xeroderma pigmentosum (XP) cells, which are deficient in excision repair, than in HeLa cells. Therefore, contrary to expectations, the use of a repair-deficient cell did not increase the sensitivity of the test. The sister chromatid exchange test for mutagens is more sensitive than the DNA synthesis inhibition test, but it takes longer and requires more specialized skills. Assays for unscheduled DNA synthesis are much less sensitive to intercalating agents, such as adriamycin, and to x-rays than are assays for inhibition of DNA synthesis. For routine screening procedures, it is suggested that the DNA synthesis inhibition assay be combined with the in vivo DNA synthesis inhibition test with mouse testes. (17 refs)

- 79-0227 Absence of Mutagenicity of Praziquantel, a New, Effective, Anti-schistosomal Drug, in Bacteria, Yeasts, Insects and Mammalian Cells.** (Eng) Bartsch, H. (Unit Chemical Carcinogenesis, International Agency Res. Cancer, Lyon, France); Kuroki, T.; Malaveille, C.; Lo-

prieno, N.; Barale, R.; Abbondandolo, A.; Bonatti, S.; Rainaldi, G.; Vogel, E.; Davis, A. *Mutat Res* 58(2/3): 133-142; 1978.

The antischistosomal drug Praziquantel (PQ: 2-cyclohexyl-carbonyl-[1,3,4,6,7,11b]-hexahydro-2H-pyrazine [2,1-a] isoquinoline-4-one) was tested for its ability to produce genetic effects in various in vivo and in vitro short-term tests with and without metabolic activation. In the plate-incorporation assay with *Salmonella typhimurium* strains TA100 and TA98, reversion frequency was not increased with PQ concentrations up to 2 mM. At 5 mM, there was no increase in forward mutations in *Schizosaccharomyces pombe* at five adenine loci, and there were no mitotic gene conversions at the *ade2* or *trp5* loci in the D₁ strain of *Saccharomyces cerevisiae*. In a host-mediated assay utilizing male Swiss albino mice, 600 mg/kg did not increase forward mutation frequency in *S. pombe* or *S. cerevisiae* injected iv. At 5 mM, PQ induced no DNA lesions that led to DNA repair in human hetero-ploid cells, as measured by unscheduled incorporation of ³H-thymidine. In V79 Chinese hamster cells, 1 mM did not induce sister chromatid exchanges, toxicity, or 8-azaguanine- or ouabain-resistant mutants and 3 mM did not induce 6-thioguanine-resistant mutants. Finally, 1.25-5 mM PQ induced only 30 X-linked recessive mutations in *Drosophila melanogaster* out of 11,788 gametes tested, a rate equal to the spontaneous mutation frequency. These results prove that the antischistosomal effectiveness of PQ is not related to mutagenic activity. (37 refs)

- 79-0228 Deuterium Isotope Effects in Mutagenesis by Nitroso Compounds.** (Eng) Elespuru, R. K. (Frederick Cancer Res. Center, Cancer Biology Program, P.O. Box B, Frederick, MD, 21501). *Mutat Res* 54(3): 265-270; 1978.

The effects of deuterium on the ability of nitrosamines (which require activation by rat liver microsomes) and nitrosamides (which act directly) to induce reversion of a nonsense mutation in the *tyr* locus of *Escherichia coli* WU 3610 was studied. Both cyclic (nitrosomorpholine and dinitrosopiperazine) and open-chain (dimethylnitrosamine) nitrosamines containing deuterium induced only about half as many mutations as did unsubstituted compounds. In contrast, the deuterium-containing nitrosamides were indistinguishable from the unsubstituted analogs (N-methyl-N'-nitro-N-nitrosoguanidine and methylnitrosourea) in mutagenic effectiveness. Deuterium also did not affect the mutagenicities of the nitrosamides in *Haemophilus influenzae*. The results suggest that the metabolic activation of nitrosamines to a mutagenic species involves the loss of hydrogen, a reaction which the nitrosamides, in the absence of enzyme, do not undergo. (10 refs)

- 79-0229 Pancreatic Carcinogenesis and Naturally Occurring Pancreatic Neoplasms of Rats and Mice**

in the NCI Carcinogenesis Testing Program. (Eng) Milman, H. A. (Toxicology Branch, Carcinogenesis Testing Program, NCI, NIH, Bethesda, MD, 20014); Ward, J. M.; Chu, K. C. *J Environ Pathol and Toxicol* 1(6): 829-840; 1978.

The carcinogenicity of 2,4-dichloro-1-(4-nitrophenoxy)benzene (nitrofen: NF) and of azinphosmethyl (APM) to the pancreas in Osborne-Mendel (OM) rats is reported, and the rat and mouse as potential animal models for the study of pancreatic carcinogenesis were compared. Of > 200 chemicals examined in a bioassay system over a 2-yr period, only NF significantly increased the incidence of exocrine pancreatic adenocarcinomas (in female OM rats only), and only APM significantly increased the incidence of islet cell tumors (in OM rats only). The experiments involved administration (feeding, injection, or gavage) of the test chemicals at the max tolerated dose (MTD) and half the MTD to OM or Fischer 344 rats and B6C3F1 mice for 52-90 wk. After 78 wk of feeding NF in the diet to OM rats and B6C3F1 mice, a slightly significant increase in the incidence of exocrine pancreatic neoplasms was observed only in female OM rats (14% incidence with MTD). After 80 wk of feeding APM to OM rats and B6C3F1 mice, a significant increase in the combined incidence of islet cell adenoma or carcinoma was seen only in male rats receiving the MTD. These results suggest that the OM or Fischer 344 rat and B6C3F1 mouse may not be sensitive models for detecting chemically induced pancreatic neoplasms or that few pancreatic carcinogens were among the 200 chemicals tested. To test the latter hypothesis, the numbers of observations of neoplasms of the exocrine or endocrine pancreas were pooled by species, strain, and sex and compared with the pooled, observed incidence in controls. With the exception of adenocarcinoma of the pancreas of female OM rats, the major exocrine pancreatic neoplasms occurred primarily in male OM or Fischer 344 rats. However, the incidence was not significantly different from that seen in controls. Islet cell adenomas or carcinomas were significantly elevated in male Fischer 344 rats vs controls and treated female Fischer 344 rats, suggesting that male Fischer rats may be a suitable model for detecting chemically induced endocrine pancreas tumors. These tumors were also significantly elevated in treated male OM rats over their female counterparts but not over controls. The data suggest that male rats may be a sensitive model for endocrine but not exocrine pancreatic neoplasms. (18 refs)

79-0230 Chloroperoxidase-catalysed Oxidation of 4-Chloroaniline to 4-Chloronitrosobenzene. (Eng) Corbett, M. D. (Rosentiel Sch. Marine and Atmospheric Sci., Univ. Miami, 4600 Rickenbacker Causeway, Miami, FL, 33149); Chipko, B. R.; Baden, D. G. *Biochem J* 175(2): 353-360; 1978.

The chloroperoxidase (CPO)-catalyzed oxidation of 4-chloroaniline to 4-chloronitrosobenzene was studied. Incubation of the aniline with CPO and H₂O₂ resulted in the rapid formation of 4-chloronitrosobenzene. The optimum pH for the ini-

tial velocity of the reaction was 4.4, the catalytic center activity was 312/min, and the apparent K_m was 8.1 x 10⁻⁴ M for 4-chloroaniline. Both bromide and chloride anions accelerated the initial rate of the reaction, but they were not incorporated into the product. 4-Chlorophenylhydroxylamine was converted into the nitroso compound even more rapidly than was 4-chloroaniline. A reaction mechanism is proposed on the basis of the currently accepted theory for the catalytic action of CPO. The metabolism of anilines by CPO might serve as a model for the metabolic disposition of aniline pollutants in the marine environment. (38 refs)

79-0231 Mutagenicities of Styrene Oxide Derivatives on *Salmonella typhimurium* (TA 100). Relationship Between Mutagenic Potencies and Chemical Reactivity. (Eng) Sugiura, K. (Dept. Chemistry, Gakushuin Univ., Toshima-ku, Tokyo 171, Tokyo, Japan); Kimura, T.; Goto, M. *Mutat Res* 58(2/3): 159-165; 1978.

The lethal and mutagenic effects of *p*-methyl-, *m*-chloro-, *p*-chloro-, and unsubstituted styrene oxide (SO) on *Salmonella typhimurium* TA 100 were investigated. At equal concentrations, *p*-chloroSO was more lethal than *p*-methyl-, *m*-chloro- or unsubstituted SO. When the survival fraction was 0.8 or more, the mutagenicities of these compounds increased in the order: *m*-chloroSO oxide = *p*-chloroSO < SO < *p*-methyl-SO. The mutagenicities of these compounds depended only on the reactivity of their benzylic site; the reactivity at their primary site and their partition coefficients appeared to have no effect. (14 refs)

79-0232 Mutagenicity of Benzotrichloride and Related Compounds. (Eng) Yasuo, K. (Mitsubishi-Kasei Institute Toxicological, Environmental Science, 1000 Kamoshida, Midori-ku, Yokohama, Japan 227); Fujimoto, S.; Katoh, M.; Kikuchi, Y.; Kada, T. *Mutat Res* 58(2/3): 143-150; 1978.

Benzotrichloride (BTC), benzal chloride (BDC), benzyl chloride (BC), and benzoyl chloride (BOC) were tested for their mutagenicity in rec-assays using *Bacillus subtilis* and reversion assays using *Escherichia coli* WP2 and Ames *Salmonella typhimurium* TA strains, with or without metabolic activation in vitro. BTC and BDC required metabolic activation for their mutagenic activities in several strains of *E. coli* and *S. typhimurium*. Mutagenic BTC and BDC metabolites did not appear to be produced by hydrolysis. BC was weakly mutagenic without metabolic activation, but BOC exhibited no mutagenic activity in any assay. The mutagenic metabolite of BTC was unstable under the experimental conditions, but it was thought to be an intermediate between BTC and benzoic acid. *E. coli* WP2 *try hcr* was more sensitive than *E. coli* B/r WP2 *try (hcr +)* to the mutagenicity of BTC. (15 refs)

79-0233 Carcinogenic Activity of Aniline Dyes and Detection of Carcinogens in the Tissues. (Rus)

Korosteleva, T. A. (N. N. Petrov Res. Inst. Oncology, Leningrad, USSR); Skachkov, A. P.; Kondrat'eva, A. F. *Gig Tr Prof Zabol* (10): 22-26; 1978.

The carcinogenic activity of three dyes used in the textile industry was studied in random-bred rats and DBA mice. Rats were divided into two groups: group 1 was subjected to daily administration of fast violet C 100% dye (K1; 0.25-0.33 g/kg); group 2 received fast violet C 200% dye (K2; 0.25-0.33 g/kg). Mice were subjected to daily administration of fast black C 200% dye (K3; 0.4 g/kg). Dye K1 contained the benzidine group, and dyes K2 and K3 contained groups similar to 2-naphthylamine (2-NA). Some of the animals were sacrificed on days 4, 15, 30 and 60 after the initiation of the experiment, and the presence of benzidine and 2-NA haptens in various tissues was assessed by means of antisera against the heterologous antigens. The tissues of rats treated with K2 and mice treated with K3 did not contain benzidine or 2-NA, while rats treated with K1 contained antigen in the liver and kidneys (rats treated with dye for 30-60 days also had antigen in the sera and spleen). Of 47 rats who received K1 until natural death, only 18 survived 500 days of the experiment: 4/18 rats had nephrosclerosis, 4 had focal proliferation of the biliary ducts and precancerous diffuse hyperplasia of liver parenchyma and stroma, 2 developed leukemia, and 3 had renal cell carcinoma and plasmocytoma of the kidney. Of 43 rats treated with K2, 19 survived 500 days of the experiment: 2/19 rats developed acute liver dystrophy, and 1 had cirrhosis. (11 refs)

79-0234 Hairy-Cell Leukemia in a Subject Exposed to Benzene. (Fre)

Dally, S. (Clinique toxicologique, Hopital Fernand-Widal, 200, rue du Fg-St-Denis, 75475 Paris Cedex 10, France); Millet, B.; Gaultier, M. *Arch Mal Prof* 39(7/8): 487-488; 1978.

Hairy-cell leukemia was diagnosed in a man who was occupationally exposed to toluene, xylene, lead, titanium, and asbestos for 13 yr. Hairy cells accounted for 26% of the leukocytes at the time of diagnosis, and for 56% 6 mo later. It is impossible to ascertain a causal relationship between hairy-cell leukemia and exposure to benzene, because the patient was not exposed directly to this solvent, and it is impossible to establish retrospectively the benzene level in the toluene to which he was exposed. (no refs)

79-0235 Activity of Acid and Alkaline Phosphatase in Neutrophils of Rats Exposed to Benzene and Treated with Selenium. (Eng)

Moszczynski, P. (Provincial Immunological Lab., Kosciuszki St. 33, Pl-32-800 Brzesko, Poland); Starek, A.; Czarnobilski, Z.; Aleksandrowicz, J. *Folia Haematol (Leipz)* 105(4): 489-496; 1978.

The effects of two dosage levels of selenium on acid phosphatase (AcP) and alkaline phosphatase (AP) activity in peripheral blood neutrophils were evaluated in rats chronically exposed to benzene vapor. Male Wistar rats were given a single dose of 1.0 or 5.0 $\mu\text{g/kg}$ Se po 10 days before the start of benzene exposure (1,200 mg/cm^3 , 6 hr/day, 6 days/wk, for 12 wk). In animals exposed to benzene only, there was an increase in AcP and a decrease in AP in the neutrophils that correlated with exposure time and persisted for as long as 5 mo after exposure. Administration of 1.0 $\mu\text{g/kg}$ Se before benzene exposure prevented these enzymatic alterations. Administration of 5.0 $\mu\text{g/kg}$ Se, however, only prevented the decrease in AP activity and caused reactive neutrophilic leukocytosis. These results indicate the need for further studies of the effects of Se on immune reactions and its possible use in prophylaxis in persons professionally exposed to benzene and its homologs. (29 refs)

79-0236 A Case of Aplastic Anemia Presumably Related to Benzene Exposure Terminating in Acute

Myelogenous Leukemia with Myelofibrosis. (Jpn) Iwata, N. (Third Dept. Internal Medicine, Gunma Univ. Sch. Medicine, Maebashi, Gunma 371, Japan); Omine, M.; Tsuchiya, J.; Maekawa, T. *Jpn J Clin Hematol* 19(9): 1234-1240; 1978.

A 27-yr-old man who had been exposed to benzene for 8 yr was admitted with a diagnosis of aplastic anemia. He achieved hematologic remission 6 mo later following treatment with testosterone and oxymetholone. Three yr after resuming the occupational use of benzene, anemia and hemorrhagic diathesis recurred. On readmission, mild lymphadenopathy, but no hepatosplenomegaly, was noted. In addition to severe anemia and thrombocytopenia, a small number of myeloblasts and atypical monocytes were observed in the peripheral blood smear. Biopsy specimen of the bone marrow, which could not be aspirated, demonstrated a marked increase of fibrous tissue. A diagnosis of acute myelogenous leukemia (AML) with bone marrow fibrosis or acute myelofibrosis was suspected. Hepatosplenomegaly appeared gradually, and the atypical immature granulocytes increased in the peripheral blood, terminating in overt AML 1 yr after the second admission. Autopsy revealed hypercellular bone marrow infiltrated with leukemic cells. It is suggested that the prolonged exposure to benzene may play a causal role in the development of aplastic anemia and the subsequent transformation into AML associated with myelofibrosis. (14 refs)

79-0237 N,N-Diethyl-4-aminoazobenzene (DEAB): Acute Actions with Respect to Possible Carcinogenicity as Well as the Role of Solvents. Morphological and Pharmacological Investigations. (Eng)

Danz, M. (Pathologisches Institut der Friedrich-Schiller-Universitat, Ziegmuhlenweg 1, DDR-69 Jena, E. Germany); Klinger, W.; Muller, D.; Kleeberg, U.; Glockner, R.; Ziebarth, D.; Urban, H. *Exp Pathol (Jena)* 16(1-6): 245-253; 1978.

The acute effects of the noncarcinogenic azo dye N,N-diethyl-4-aminoazobenzene (DEAB) were investigated in male and female Sprague-Dawley (SD) and male Wistar (Wi) rats. The rats were given 50, 66, or 70 mg/kg DEAB dissolved in dimethyl sulfoxide (DMSO) or sunflower oil via stomach tube and sacrificed 48 hr later. In a separate experiment, the influence of various solvents on the excretion of DEAB and the potent hepatocarcinogen N,N-dimethyl-4-aminoazobenzene (DAB) was investigated in male Wi rats. DEAB was hepatotoxic to all rats receiving 66 or 70 mg/kg; it produced dose-dependent functional changes and slight structural alterations in the liver. The threshold dose for damage to hepatocytes was 50 mg/kg, as there was no liver cell death with this dose. The adrenocortical response to DEAB was dependent on solvent and rat strain. Adrenal mitoses were increased significantly in SD rats only when DEAB was dissolved in DMSO. Both solvents were effective in Wi rats, with the oil being more effective than DMSO. The cytochrome P-450-dependent N-demethylation of ethylmorphine and cytochrome P-448-dependent aryl hydrocarbon hydroxylation were inhibited by DEAB independently of the solvent used. In contrast, the hepatic N-demethylation of dimethylnitrosamine was reduced only by DEAB dissolved in oil. DMSO alone or with DEAB increased DMN N-demethylation 50% compared with oil-treated or untreated controls. The excretion of DEAB and DAB was delayed and the total amount excreted was reduced when the substances were dissolved in DMSO. The similarity of the results obtained with DEAB to those obtained with DAB and other carcinogens indicates that DEAB may also prove to be carcinogenic upon long-term testing. (31 refs)

79-0238 Promotion by Dietary Phenobarbital of Hepatocarcinogenesis by 2-Methyl-N,N-dimethyl-4-aminoazobenzene in the Rat. (Eng) Kitagawa, T. (Dept. Pathology Cancer Inst., Tokyo 170, Japan); Pitot, H. C.; Miller, E. C.; Miller, J. A. *Cancer Res* 39(1): 112-115; 1979.

The hepatocarcinogenicity of 2-methyl-N,N-dimethyl-4-aminoazobenzene, previously shown to be noncarcinogenic in adult rats in the absence of further treatment, was observed by following a 1- to 6-wk period of feeding this dye (0.06% of diet) to weanling male Donryu rats with the dietary administration of 0.5% phenobarbital up to 70 wk. Many large hepatocellular carcinomas developed in the phenobarbital-treated animals by 72 wk, whereas only a very small number of tiny neoplastic nodules, including one carcinoma, were seen in the rats not given this drug. This study suggests that the use of promoting agents, following the short-term administration of weak hepatocarcinogens, can be useful in demonstrating the initiating activity of such compounds. This system may be useful in identifying these agents in the environment. (21 refs)

79-0239 Enhancing Effect of Phenobarbital on the Development of Enzyme-Altered Islands and

Hepatocellular Carcinomas Initiated by 3'-Methyl-4-(dimethylamino)azobenzene or Diethylnitrosamine. (Eng) Kitagawa, T. (Dept. Pathology, Cancer Inst. Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170, Japan); Sugano, H. *Gann* 69(5): 679-687; 1978.

The effect of dietary phenobarbital (PB: 0.05%) on the development of enzyme-altered islands (EAI) and hepatocellular carcinomas initiated by short-term treatment with 3'-methyl-4-(dimethylamino)azobenzene (3'-Me-DAB) or diethylnitrosamine (DENA) was studied in male Donryu rats. PB generally enhanced the proliferation of carcinogen-induced EAI, so that the number and size of EAI were much larger in phenobarbital-fed groups by wk 12 than in control groups kept on a basal diet. The growth rate of EAI, however, was not uniform and only a small minority progressed to large islands or carcinomas. In rats fed a diet containing 0.06% 3'-Me-DAB for 3 wk, the enhancing effect of PB on cancer induction was remarkable by wk 36; but in rats fed 0.06% 3'-Me-DAB for 1 wk, no cancer developed by wk 60, although a large number of small EAI appeared. Thus, a summation effect of the carcinogen was observed even when it was given for a short period as an initiator. The enhancing effect of PB was also marked in rats initiated by DENA (2 mg ip); however, a considerable number of carcinomas also developed in control rats given ip DENA + a basal diet. Most of the DENA-initiated tumors were trabecular carcinomas, but approx 40% of the 3'-Me-DAB-initiated tumors were adenocarcinomas. The carcinogen-induced and EAI populations differed in that the DENA induced cells showed a greater potential to progress to carcinomas. (23 refs)

79-0240 Changes in Toxicity and Carcinogenicity of N-Methyl-N-Nitrosobenzylamine in Rats by Methyl Substitution on the C-Atoms Adjacent to the Nitrogen. (Ger) Schweinsberg, F. (Hygiene-Institut der Universität, Silberstrasse 7, D-7400 Tübingen, W. Germany); Kouros, M.; Manncke, K.; Rieth, K. *Z Krebsforsch* 92(3): 235-241; 1978.

The effect of methyl-substitution on the C-atom alpha to the N atom on the carcinogenicity and toxicity of N-nitroso-N-methyl-benzylamine (NMBA) in SIV 50 female rats was studied. NMBA selectively produces tumors in the esophagus and pharynx of rats; oxidation of the proton on the alpha C-atom is thought to be the first step in formation of the ultimate carcinogen. In the acute toxicity studies, the compound was given in one dose in edible oil by stomach tube. These rats (av wt, 200 g at dosage time) were weighed daily for 2 wk. For the long-term studies, rats with an av starting wt of 120 g were given one compound in their drinking water at 10, 15, or 30 ppm. The previously published LD₅₀ for NMBA is 18 mg/kg. For N-nitroso-N-methyl-(1-phenyl)-ethylamine (NMPE) the LD₅₀ was 600 mg/kg; for the N-nitroso-N-methyl-2-(2-phenyl)-propylamine derivative (NMPP), the LD₅₀ was 2,100 mg/kg; for N-nitroso-N-ethyl-benzylamine (NEB), the LD₅₀ was 250 mg/kg. None of the

rats given NMPP showed any sign of the cancerous changes associated with NMBA. They were observed for 23 mo. Rats given NEB at 30 ppm began to show symptoms (wt loss, respiratory difficulty) at 4.5 mo. Those given NMPE at 30 ppm showed similar symptoms at 8.5 mo. The rats given NEB or NMPE were observed until death. All of them had precancerous or cancerous changes of the esophagus. The lesions resembled keratinizing squamous cell papillomas with partial malignant degeneration. Thus NMPE possesses carcinogenicity with the same distribution of sites as given by NMBA; symptoms appeared later with NMPE. Steric hindrance of enzymatic attack on the H atom remaining on the alpha-C can explain this result. The ultimate carcinogen cannot be formed from NMPP because no proton remains on the alpha-C; thus NMPP is no longer carcinogenic under the selected conditions and has a low acute toxicity. Oxidation of a proton on the alpha-C can occur in NEB, and this compound is carcinogenic, as expected. Different effects of substituents on the carcinogenicity and acute toxicity of a compound may result from the many different mechanisms by which a compound may be toxic. (8 refs)

79-0241 Histopathology of the Rat Liver Following a Single Autoprotective Dose of 3'-Methyl-4-dimethylaminoazobenzene. (Eng) Flaks, A. (Cancer Res. Unit, Dept. Biology, Univ. York, Heslington, York YO15DD, England); Flaks, B. *J Pathol* 126(2): 71-78; 1978.

The possible carcinogenic or other persistent effects of a single 1.2 g/kg po dose of 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB) were investigated in 95 Leeds rats. Two rats were killed and examined histologically at 24, 48, and 72 hr, and 3, 5, and 7 days after treatment, after which three rats were killed at weekly intervals up to 42 days, and the remaining rats were killed in groups at 3, 4, 8, 12, and 14 mo after treatment. Glycogen depletion was evident in centrilobular zones at 24 hr, and whole lobes were involved at 48 hr. There was no significant recovery in glycogen stores until 21 days, and for the duration of the experiment most hepatocytes were lacking normal glycogen stores. Hepatocellular necrosis was evident at 3 days, but resolved by 7 days. Hepatocytes that did not become necrotic were of variable size, some containing giant nuclei and displaying a mild degree of regenerative hyperplasia; normal morphology was usually not recovered over the duration of the experiment. Oval cells with large pale nuclei appeared at 3 days; they proliferated to involve whole lobules and distorted liver architecture at 14 days, but largely disappeared by 35 days. Hepatic parenchymal cells contained numerous small lipid and hyaline inclusions up to 7 days. From 4 mo onward, there was a progressive increase in the abundance of "clear cells". Although no tumors were found in these animals, it appears that a single dose of 3'-MeDAB can induce histopathological changes in rat livers similar to those seen in carcinogenesis, while avoiding severe toxic damage and permitting long-term survival in most animals. (27 refs)

79-0242 Cytogenetic Effects of Styrene and Styrene Oxide. (Eng) Linnainmaa, K. (Dept. Industrial Hygiene, Toxicology, Inst. Occupational Health, Helsinki, Finland); Meretoja, T.; Sorsa, M.; Vainio, H. *Mutat Res* 58(2/3): 277-286; 1978.

The cytogenetic effects of styrene (S) and styrene oxide (SO) were compared in human lymphocyte cultures and root-tip cells of the onion *Allium cepa*, caused chromosome breaks in both test systems, and in *Allium* it had a strong c-mitotic effect. SO, on the other hand, appeared to destroy the tertiary folding of chromatin. The cytotoxicity of SO was very high (complete mitotic inhibition occurred at 0.03% volume solute/volume solvent) in human lymphocytes, but S was slightly more toxic than SO in *Allium*. Styrene glycol, another SO metabolite did not cause mitotic inhibition. (15 refs)

79-0243 The Expression Curve of Mutants Induced by Styrene Oxide at the HGPRT Locus in V79 Cells. (Eng) Bonatti, S. (Laboratorio di Mutagenesi e Differenziamento del CNR, Pisa, Italy); Abbondandolo, A.; Corti, G.; Fiorio, R.; Mazzaccaro, A. *Mutat Res* 52(2): 295-300; 1978.

The decrease in the frequency of 8-azaguanine (AG)- and 6-thioguanine (6TG)-resistant clones induced by styrene oxide (SO) in V79 Chinese hamster cells after a max had been reached was investigated. Twenty-seven AG- or 6TG-resistant clones were isolated at 90 hr (Group 1) or 210 hr (Group 2). All isolates showed cross-resistance and maintained the resistant phenotype during subsequent cultivation in the absence of either selective drug. The spontaneous reversion frequency on HAT medium was $\leq 10^{-6}$ for seven Group 1 and seven Group 2 clones. In a group of 18 mutants induced by ethyl methanesulfonate (EMS), 9 reverted with comparable low frequency. Thus, the resistant phenotype of clones appearing at the time of max expression (90 hr) is not unstable. The cloning efficiency of Group 1 mutants was poor: for 7/13 mutants, the colony forming ability was $< 50\%$. The same was true for only two Group 2 mutants, a statistically significant difference. Moreover, the growth curves of four Group 1 isolates showed that they all grew at a lower rate than that of the parental cells. Thus, the SO-induced resistant clones were likely outgrown by wild-type cells during cultivation in unselective medium. The reason for the low division rate in SO-induced mutants is not known. In addition, 11/24 Group 1 and 2 clones analyzed showed $> 5\%$ polyploid cells vs only 1 clone among 18 EMS-induced mutants. It is not known whether the incidence of polyploid cells was causally related to the decline of the expression curve. (5 refs)

79-0244 Mutagenicities of Phenacetin and Its Metabolites. (Eng) Shudo, K. (Faculty Pharmaceutical Science, Univ. Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113,

Japan); Ohta, T.; Orihara, Y.; Okamoto, T.; Nagao, M.; Takahashi, Y.; Sugimura, T. *Mutat Res* 58(2/3): 367-370; 1978.

The mutagenicity of phenacetin and its metabolites was tested in *Salmonella typhimurium* strains TA100 and TA98 with and without microsomal activation. Phenacetin itself exerted no mutagenicity on either strain with or without activation. N-Hydroxyphenacetin (N-OH-Ph) with microsomal activation was mutagenic to TA100 but not to TA98; it was not mutagenic to either strain without activation. N-Acetoxyphenacetin (N-OAc-Ph) was mutagenic to both TA100 and TA98 with activation but to neither strain without activation. N-Acetylbenzoquinone imine had no mutagenic activity on either strain, with or without microsomal activation. These results indicate that N-OAc-Ph is a more proximate mutagen than is N-OH-Ph, since it is mutagenic to TA98, which is not susceptible to N-OH-Ph. However, N-OAc-Ph is not an ultimate mutagenic form since it still required metabolic activation. (16 refs)

79-0245 Fluoroxene Mutagenicity. (Eng) Baden, J. M. (Dept. Anesthesia, Stanford Univ. Sch. Medicine, Stanford, CA); Kelley, M.; Simmon, V. F.; Rice, S. A.; Mazze, R. I. *Mutat Res* 58(2/3): 183-191; 1978.

The volatile anesthetic fluroxene (FL) (2,2,2-trifluoroethyl vinyl ether), which contains the stabilizer N-phenyl-1-naphthylamine, was tested for mutagenicity in *Salmonella typhimurium* strains, TA1535, TA1537, TA98 and TA100, and *Escherichia coli* strain, WP2. In addition, purified FL; N-phenyl-1-naphthylamine; trifluoroethanol (a major FL metabolite), and urine from rats anesthetized with FL were tested. Several procedures were used, including exposure of bacteria to vapor in desiccators and in liquid suspension. FL, but not its stabilizer, was mutagenic to strains TA1535, TA100, and WP2 only in liquid suspension and only in the presence of a rat-liver enzyme system. Trifluoroethanol and urine from FL-treated rats were not mutagenic to any strain of bacteria. These findings indicate that FL is a promutagen that requires preincubation before it is recognized. Further experiments were performed with enzymes prepared from mouse, hamster and human liver. FL was mutagenic only in the presence of enzymes from Aroclor 1254-pretreated rodents. Since FL was not mutagenic in the presence of enzymes from three human livers, the significance of these findings for humans are unclear. However, the possibility that FL has contributed to the increased incidence of malignancies in operating personnel cannot be excluded. (17 refs)

79-0246 Phenyl-beta-naphthylamine. (Eng) Garfinkel, L. (Dept. Epidemiology and Statistics, American Cancer Society, New York, NY). *CA* 28(2): 116; 1978.

The higher risk of bladder cancer and leukemia in rubber

industry workers cannot be attributed to phenyl- β -naphthylamine, as these workers are exposed to several other chemicals, notably benzene. (no refs)

79-0247 Carcinoma of the Larynx in Naphthalene Distillation Workers. (Ger) Wolf, O. (Hals-Nasen-Ohren-Klinik, Bezirkskrankenhaus Dessau, Auenweg 38, DDR-4502 Dessau-Alten, E. Germany). *Z Gesamte Hyg* 24(10): 737-739; 1978.

Four of 15 male naphthalene distillation workers from one chemical plant developed laryngeal carcinoma, an abnormal incidence compared with that in the general male population in East Germany (6.3/100,000). The workers had been exposed to naphthalene sublimate and tar vapors. The length of the occupational exposure was 7-31 yr, the latent period 13-32 yr. All four patients were smokers. Solid immature squamous cell carcinoma, pleomorphic undifferentiated carcinoma, and keratinizing and nonkeratinizing squamous cell carcinomas were found. The findings indicate the occupational hazards of exposure to naphthalene and tars. (9 refs)

79-0248 Photodegradation of 3,3'-Dichlorobenzidine. (Eng) Banerjee, S. (Life Sciences Div., Syracuse Res. Corp., Merrill Lane, University Heights, Syracuse, NY, 13210); Sikka, H. C.; Gray, R.; Kelly, C. M. *Environ Sci Technol* 12(13): 1425-1427; 1978.

The photodegradation of 3,3'-dichlorobenzidine (DCB) and 3-chlorobenzidine was studied. Irradiation of aqueous solutions of DCB resulted in sequential degradation to monochlorobenzidine (MCB) and benzidine and to the formation of more than five relatively water-insoluble products that appeared to be dimers or higher analogues of DCB and/or its photoproducts. Irradiation of DCB in noonday sunlight confirmed the expected photolability of DCB. Disappearance quantum yields for DCB and MCB were high, whereas that for benzidine was much lower. Virtually no degradation occurred following irradiation of DCB in hexane, 2-propanol, or methanol. The photoreduction of DCB appears to involve a mechanism different from simple homolysis of the carbon-chlorine bond. Proton transfer appears to be involved and the dechlorination process may proceed through an ionic pathway involving the loss of chloronium ion from the excited DCB molecule. (15 refs)

79-0249 Modified Method for Determination of Urinary Benzidine. (Eng) Dangwal, S. K. (Central Labor Inst., Sion, Bombay 400 022, India); Kadam, V. T.; Jethani, B. M. *Am Ind Hyg Assoc J* 39(12): 1019-1022; 1978.

An analytical method for the determination of urinary benzidine is presented. The method is based on the colorimetric

estimation of the yellow merquinodal complex formed by the reaction of solvent-extracted benzidine with chloramine T. If samples were preserved and adjusted to pH 7.5 with HCl, precipitate formation was prevented, and the av percentage recovery of benzidine was 80%. (5 refs)

- 79-0250 Effects of Carcinogenic and Noncarcinogenic Chemicals on Nuclear DNA Synthesis Rate and Labeling Index in Growing CBA Mice. The Thymidine-Incorporation Screening System (TSS).** (Ger) Amlacher, E. (Pathologisches Institut, Friedrich-Schiller-Universität, Ziegmühlweg 1, DDR-69 Jena, E. Germany); Rudolph, C. *Exp Pathol (Jena)* 16(1-6): 69-82; 1978.

The effects of single doses of 21 carcinogenic and 9 noncarcinogenic chemicals on nuclear DNA synthesis in the renal tubular and liver epithelial cells of CBA mice were studied by a thymidine-incorporation screening system (TSS) using autoradiography. The animals were inoculated with ^3H -thymidine (3 $\mu\text{Ci/g}$ ip) 24 hr after they were administered the chemicals and killed 50 min later. Twenty of the 21 carcinogens had a significant suppressive effect on nuclear DNA synthesis; the carcinogen 1-aminophthaline and all the noncarcinogens had no such effect. Actinomycin D, a suspect carcinogen, caused a significant increase in thymidine incorporation. Among the carcinogens, nitrosamines and nitrosamides were especially active in terms of suppression of nuclear DNA synthesis. The thymidine labeling index failed to show any systematic differences between carcinogens and noncarcinogens. The findings indicate the usefulness of TSS in screening for chemical carcinogens. (46 refs)

- 79-0251 The Mutagenic Effect of Benzene, Toluene and Xylene Studied by the SCE Technique.** (Eng) Gerner-Smidt, P. (Inst. Human Genetics, Univ. Aarhus, DK-8000 Aarhus C, Denmark); Friedrich, U. *Mutat Res* 58(2/3): 313-316; 1978.

The effects of benzene, toluene, and xylene on human lymphocytes were examined in vitro with respect to changes in the rates of occurrence of sister-chromatid exchanges (SCE), structural chromosomal aberrations, and cell growth. Three concentrations of the solvents were tested: 1.52 mg/ml, 15.2 $\mu\text{l/ml}$ and 152 $\mu\text{g/ml}$. None of the chemicals tested changed the number of SCE or the number of chromosomal aberrations in the lymphocytes. The two highest concentrations of toluene and the highest concentration of xylene showed positive results in the growth inhibition test. Since benzene and toluene are known to induce chromosomal aberrations in humans and in animals, these results suggest that it is the metabolites of these compounds that are mutagenic and not the organic solvents themselves. (13 refs)

- 79-0252 Characterization of Carbon Black Adsorbates and Artifacts During Extraction.** (Eng) Fitch, W. L. (Acurex Corp., 485 Clyde Ave., Mountain View, CA, 94042); Everhart, E. T.; Smith, D. H. *Anal Chem* 50(14): 2122-2126; 1978.

Materials obtained by extraction of three commercial carbon black samples (lampblack, 2 channel black samples) with benzene and naphthalene (NT) were identified by combined gas chromatography/mass spectrometry and advanced computer techniques. Extraction of the channel blacks with benzene alone yielded oxidized polynuclear aromatic hydrocarbon (PAH) derivatives in ppm quantities, including ketones, quinones, anhydrides, and nitro compounds. When benzene/methanol mixtures were used for Soxhlet extraction of the channel blacks, PAH polycarboxylic acid methyl esters were obtained, presumably by acid-catalyzed esterification on the highly acidic surface of the black. When these carbon samples were extracted with NT, using a special apparatus designed to maintain the solvent in liquid form at elevated temperature and reduced pressure, the major extractable materials were different from those seen in the benzene extracts. They include three binaphthyls, 2 dinaphthofurans, and 2 methylbinaphthyls, believed to be formed by reaction of NT with surface groups of the carbon. A control experiment confirmed that these binaphthyls and derivatives were not adsorbed species on the channel blacks. Similar extractions of lampblack yielded PAH, but only traces of the oxidized species and none of the NT artifacts. NT was more efficient at extracting high-mol-wt PAH than benzene; the lower mol-wt PHA were partially lost during NT distillation. (30 refs)

- 79-0253 Comparative Studies of the Carcinogenic Polycyclic Aromatic Hydrocarbons in the Environment.** (Hun) Kertesz, M. (Országos Kozegészségügyi Intézet, Budapest, Hungary); Horvath, A.; Kiss, A.; Morlin, Z.; Toth, B.; Heszina, A. Ja.; Smirnov, G. A.; Shabad, L. M. *Egészségtudomány* 22(3): 245-252; 1978.

Polycyclic aromatic hydrocarbon concentrations in the air and soil were measured in different areas in Hungary. The concentrations were highest in center city Budapest and lowest in suburban and recreational areas. Phenanthrene, fluoranthene, pyrene, chrysene, benz(a)anthracene, benz(b)fluoranthene, perylene, benzo(e)pyrene, benz(a)pyrene, benzo(ghi)perylene, benzo(rst)pentaphene, dibenz(a,i)anthracene, dibenz(a,h)anthracene, and coronene were found. (12 refs)

- 79-0254 The Effect of Some Cigarette Smoke Constituents and Other Compounds on the Metabolism of Benzo(a)pyrene in Rabbit Lung 9000g Supernatant.** (Eng) Hulshoff, A. (Farmaceutisch Laboratorium van de Rijksuniversiteit, Catharijnesingel 60, Utrecht, The Netherlands);

Lubawy, W. C.; Kostenbauder, H. B. *Xenobiotica* 8(11): 711-717; 1978.

The inhibitory effects of a number of compounds, some of which occur in cigarette smoke, on benzo(a)pyrene (BP)-metabolizing enzymes were studied in lung homogenates (9,000 x gravity supernatant) of 3-methylcholanthrene (MC)-treated and control rabbits. BP (0.8 nmol) was incubated with the homogenate and various concentrations of each inhibitor for 15 min. BP and its metabolites were determined by liquid scintillation counting. MC treatment caused a six-fold increase in metabolic activity compared with homogenates from untreated rabbits. Of the cigarette smoke constituents tested, naphthalene, naphthol, and anthracene were the most potent inhibitors of the BP-metabolizing enzymes. Nicotine and phenol were somewhat less active in this respect. The results suggest that, in the case of some of the structurally related compounds, the more lipophilic ones are also the more active inhibitors. The inhibitors could be divided into two groups on the basis of mode of action: (1) those inhibiting primarily benzo(a)pyrene hydroxylase activity (phenol, 1-naphthol, nicotine, and acetone) and (2) those inhibiting the activity of both the epoxide-metabolizing enzymes and BP hydroxylase (naphthalene, anthracene, and chlorpromazine). The most active inhibitors (anthracene, naphthol, and chlorpromazine) also caused a significant decrease in the amount of BP bound covalently to tissue macromolecules. These results indicate that the data obtained with the frequently used fluorescence technique for determining BP-hydroxylase activity, can be misleading when used for determining changes in BP metabolism with certain inhibitors. (33 refs)

79-0255 Hansch Analysis, Free Wilson Analysis, and Sub-structure Analysis. (Eng) Craig, P. N. (Franklin Inst., Philadelphia, PA, 19103). In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977*. Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 63-67; 1978.

The purpose of structural correlation analysis is to develop a mathematical relationship between chemical structure (or physical properties) and biological effect in order to predict the activities of untested compounds. The Hansch approach assumes that one or at most a few parameters are of importance. Through multiple regression analysis computer programs, an attempt is made to correlate all possible combinations of these parameters with the desired biological response. Regression analyses of a series of structurally related compounds may give a linear relationship between a parameter and biological activity or equations involving parabolic terms or steric constants. The basic assumption of the Free-Wilson method is that each time a substituent group appears in the same substituent group position, it makes a constant contri-

bution to the overall biological activity of the molecule; the only variables are the activity and the chemical structure. Results of analyses of the same series of antimalarial phenanthrenes revealed that the Hansch and Free-Wilson methods paralleled each other. Although modification is necessary for application of these methods estimating the carcinogenicity and mutagenicity of compounds, the methods show promise for this purpose. (7 refs)

79-0256 Methylbenz(a)anthracenes: Correlations Between Theoretical Reactivity Indices and Carcinogenicity. (Eng) Smith, I. A. (Dept. Chemistry, Wright State Univ., Dayton, OH, 45435); Seybold, P. G. *Int J Quant Chem Quant Biol Symp* (5): 311-320; 1978.

The presumed in vivo metabolic transformations of methylbenz(a)anthracene (MBA) compounds were examined using orbital reactivity indices, in order to explain the differences in the carcinogenic activity (CA) of the MBA's. These studies suggested that methyl substitution on the benzo ring of BA (carbons 1, 2, 3, and 4) leads to inactive derivatives, because these methyl groups hinder a reaction crucial to CA. Analogous substitutions may decrease or eliminate CA in other polycyclic aromatic hydrocarbons. When methyl substitution increases the reactivity of the B-region bond of the dihydrodiol form or increases the stability of the resulting "bay region" carbonium ion, CA is enhanced. The latter seems to be an especially accurate guide to CA. These results and those of previous studies strongly suggest that reactions leading ultimately to "bay region" carbonium ions form an important pathway for CA in these compounds. The carcinogenic reactions were susceptible to reasonably accurate analysis using reactivity indices taken from molecular orbital theory. By implication, electronic factors appear to be critical in determining the CA of polycyclic aromatic hydrocarbons, rather than enzyme specificities, solubilities, diffusion rates, or other factors that, a priori, might be expected to play strong roles. (34 refs)

79-0257 Reactions of the Carcinogens 7-Hydroxymethyl-12-methylbenz(a)anthracene and 7-Acetoxy-methyl-12-methylbenz(a)anthracene with DNA. (Eng) Flesher, J. W. (Dept. Pharmacology, Univ. Kentucky Coll. Medicine, Lexington, KY, 40506); Tay, L. K. *Res Commun Chem Pathol Pharmacol* 22(2): 345-355; 1978.

The covalent reactions of the carcinogens 7-hydroxymethyl-12-methylbenz(a)anthracene (7-HOMe-12-Me-BA) and 7-acetoxymethyl-12-methylbenz(a)anthracene (7-AcOMe-12-Me-BA) with calf thymus DNA were studied. 7-HOMe-12-Me-BA reacted poorly with DNA [2 micromoles (μ mol) hydrocarbon/mole DNA P] in the absence of enzymes, whereas 7-AcOMe-12-Me-BA reacted readily (21.4 μ mol hydrocarbon/mole DNA P). In the absence of

a PAPS generating system and ATP, 7-HOMe-12-Me-BA did not react with DNA, but in the presence of the complete system, considerable reaction occurred (27.2 μ mol hydrocarbon/mole DNA P). If sulfate ion was omitted from the reaction mixture, 22.4 μ mol hydrocarbon/mole DNA P was generated, whereas if ATP was omitted, only 0.4 μ mol/mole DNA P was obtained. If enzyme was omitted, the reaction occurred in the presence (44.8 μ mol/mole DNA P) but not in the absence of ATP. ADP was also active, although less so, whereas AMP and adenosine were inactive. The data demonstrate that ATP mediates the nonenzymatic reaction of 7-HOMe-12-Me-BA with DNA, suggesting the formation of a reactive phosphate ester. (18 refs)

79-0258 Modulation of Rat Guanylate Cyclase Activity In Vitro by Chemical Carcinogens. (Eng) Vesely, D. L. (Div. Endocrinology and Metabolism, Dept. Medicine, Univ. Miami Sch. Medicine, P.O. Box 875, Miami, FL, 33152); Lehotay, D. C.; Levey, G. S. *Enzyme* 23(5): 356-360; 1978.

Compounds from several major classes of carcinogens were examined for their effects on guanylate cyclase (GC) activity and cyclic guanosine 3',5'-monophosphate (GMP) levels in male Sprague-Dawley rat liver slices. Compounds tested were chloromethyl methyl ether (α -halo ethers), benzidine and B-naphthylamine (aromatic amines), methyl yellow (azo dyes), 1,2-benzanthracene and acridine (polycyclic hydrocarbons), aflatoxin B₁, B₂, G₁, and G₂, and N'-nitro-N-nitroso-N-propylguanidine (NNPG, nitrosamines). All of the compounds except NNPG significantly decreased GC activity in liver preparations in vitro at a concentration range of 0.5-13 millimoles (mmol)/liter. In these same preparations, NNPG (1 mmol/liter) produced a 20-fold stimulation of GC activity. None of the carcinogens had significant effects on renal or hepatic adenylate cyclase. NNPG and butadiene diepoxide (another stimulator of GC) increased cyclic GMP levels in liver slices by five- and fourfold, respectively, while benzidine and chloromethyl methyl ether decreased cyclic GMP levels by 30% and 71%, respectively. Some of the nitrosamides that increase GC activity also increase DNA synthesis, but carcinogens that decrease GC activity inhibit DNA or RNA synthesis, which suggests a relationship between cyclic GMP, DNA synthesis, and chemical carcinogens. (19 refs)

79-0259 Identification of Four trans-3,4-Dihydrodiol Metabolites of 7,12-Dimethylbenz(a)anthracene and Their In Vitro DNA-binding Activities upon Further Metabolism. (Eng) Chou, M. W. (Dept. Pharmacology, Sch. Medicine, Uniformed Services Univ. Health Sciences, Bethesda, MD, 20014); Yang, S. K. *Proc Natl Acad Sci USA* 75(11): 5466-5470; 1978.

The trans-3,4-dihydrodiols of 7,12-dimethylbenz(a)anthracene (DMBA), 7-methyl-12-hydroxymethylbenz(a)anthra-

cene (7-Me-12-OHMeBA), 7-hydroxymethyl-12-methylbenz(a)anthracene (7-OHMe-12-MeBA), and 7,12-di(hydroxymethyl)benz(a)anthracene [7,12-(OHMe)₂BA] were identified as metabolites of the potent carcinogenic and adrenocorticolytic agent DMBA. The four trans-3,4-dihydrodiols were identified by their (1) UV-visible absorption and fluorescence properties, (2) different retention times on both reversed-phase and normal-phase high-pressure liquid chromatography, (3) mass spectra, and (4) inability to form vicinal cis-acetonides. Upon further metabolism by liver microsomes, the trans-3,4-dihydrodiols of DMBA, 7-Me-12-OHMeBA, and 7-OHMe-12-MeBA were found to give rise to products that bound more strongly to DNA in vitro than the products of 7,12-Me₂BA. The evidence suggests that one or more of the four trans-3,4-dihydrodiols may be the proximate carcinogenic and adrenocorticolytic metabolites. (41 refs)

79-0260 Induction of Malignant Transformation and Mutagenesis by Dihydrodiols Derived from 7,12-Dimethylbenz(a)anthracene. (Eng) Marquardt, H. (Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Baker, S.; Tierney, B.; Grover, P. L.; Sims, P. *Biochem Biophys Res Commun* 85(1): 357-362; 1978.

7,12-Dimethylbenz(a)anthracene (DMBA) and four of its trans-dihydrodiols: trans-3,4-dihydro-3,4-dihydroxy-DMBA (3,4-diol), trans-8,9-dihydro-8,9-dihydroxy-DMBA (8,9-diol), trans-10,11-dihydro-10,11-dihydroxy-DMBA (10,11-diol), and trans-5,6-dihydro-5,6-dihydroxy-DMBA (5,6-diol) were tested for their ability to induce mutations to 8-azaguanine resistance in V79 Chinese hamster cells and malignant transformation in M2 mouse fibroblasts. The concentrations tested ranged from 0.12 to 1 μ g/ml for all compounds except the 5,6-diol, which was tested at 1, 5, and 10 μ g/ml. The 3,4-diol and the 8,9-diol, but not DMBA, induced mutations in V79 cells; both diols were more active than the parent compound in inducing malignant transformation in the M2 cells. The 5,6-diol and the 10,11-diol were relatively inactive as mutagens or transforming agents. When cells from two transformed clones of the 3,4-diol were injected into six C3H/HcJ mice, all six mice developed sarcomas 5 wk later. This evidence is consistent with the theory that the vicinal diol-epoxides are the important species in activated, carcinogenic polycyclic hydrocarbons. (22 refs)

79-0261 Acetic Acid Pretreatment of Initiated Epidermis Inhibits Tumour Promotion by a Phorbol Ester. (Eng) Murray, A. W. (Sch. Biological Sciences, Flinders Univ. S. Australia, Bedford Park, S. Australia 5042, Australia). *Experientia* 34(11): 1507-1508; 1978.

A study was conducted to determine whether the cytotoxicity of compounds such as acetic acid could be an explanation for their inability to act as tumor promoters. Female Swiss

albino mice were initiated on the skin with 25 μ g 7,12-dimethylbenz(a)anthracene (DMBA). One week later, one group was treated 2x/wk with 167 micromoles (μ mol) acetic acid and another with 500 μ mol, for a total of five doses. All groups were then promoted with croton oil (0.2 ml of a 0.5% soln 2x/wk). Pretreatment of initiated skin with five 500- μ mol doses of acetic acid gave a tumor yield during promotion of 50% that of the control (DMBA + croton oil only) group. This decrease was probably not caused by interference with DMBA initiation, since acetic acid treatment was not begun until 1 wk after DMBA application. The simplest explanation is that acetic acid treatment killed a proportion of the initiated cells. Agents such as acetic acid may induce all of the biochemical changes in skin (ie, hyperplasia) necessary for promotion but do not assay as promoters because of cytotoxicity. The observation that not all hyperplastic agents act as tumor promoters does not eliminate the possibility that epidermal hyperplasia is a sufficient condition for promotion. (6 refs)

79-0262 Preparation, Isolation, Analysis, and Characterization of 3-Benzo(a)pyrenyl- β -D-glucopyranosiduronic Acid: A Metabolite of 3-Hydroxybenzo(a)pyrene with Potentially High Carcinogenic Activity. (Eng) Johnson, D. B. (Midwest Res. Inst., 425 Volker Blvd., Kansas City, MO, 64110); Engel, J. F.; Murrill, E. E.; Guire, P. E.; Barker, C. W.; Bardwell, C. M.; Shan, A. Y.; Swanson, M. J.; Stone-Heurner, J. G. *Anal Biochem* 91(1): 138-145; 1978.

3-Hydroxybenzo(a)pyrene (3OH-BP; 1.0 mM) was converted to its glucuronide, 3-benzo(a)pyrenyl- β -D-glucopyranosiduronic acid (BGA), by incubation with 25 mg freeze-dried rabbit liver microsomes, 2.0 ml of 0.1 M tris(hydroxymethyl)aminomethane-HCl, 0.002 M $MnCl_2$, 0.01% Triton X-100, 5.0% ethanol, and 3.75 mM uridine 5'-diphosphoglucuronic acid. The reaction was monitored by fluorimetry and reverse-phase, paired-ion, high-pressure liquid chromatography (HPLC). Fluorescence loss was linear up to 120 min. HPLC of the reaction mixture gave a retention time of 5.1 min for the glucuronide peak and 36.5 min for the 3OH-BP peak with 70% methanol and 30% water as eluants. Proof of the existence of BGA was supplied by radiotracer analysis with tritium and enzymatic hydrolysis with β -glucuronidase, with both techniques utilizing HPLC. Field desorption and direct inlet mass spectral techniques were used to characterize BGA. All these methods should be readily adaptable to other glucuronide conjugates of polynuclear aromatic hydrocarbons. (10 refs)

79-0263 Serum Haptoglobin Levels in Mice with 7,12-Dimethylbenz(a)anthracene-induced Tumors. (Eng) Palmer, W. G. (NCI Frederick Cancer Res. Center, Frederick, MD, 21501); Ulland, B. M. *Oncology* 35(5): 220-223; 1978.

Serum haptoglobin (Hp) levels were determined periodically during a 24-wk period in mice treated with 7,12-dimethylbenz(a)anthracene (DMBA; 28.5 mg/kg 1x/wk for 12 wk). Thirty of 45 mice treated with DMBA developed tumors by the end of 24 wk. Thirteen of the 15 tumor-bearing males had lymphocytic lymphomas, but 12/15 tumor-bearing females had mammary carcinomas. Hp levels were normal in 448/460 serum samples collected before 10 wk, during which time there was no evidence of tumors. This indicates that DMBA itself does not affect serum Hp concentrations. Nine of the 15 DMBA-treated mice that did not develop tumors had either normal or minimally elevated Hp levels throughout the 24-wk period. Animals with lymphomas had only minimal or moderate elevations in serum Hp, whereas mice bearing mammary carcinomas and gastric squamous cell carcinomas had high Hp levels that remained elevated during most of the tumor development period. In most mice with mammary carcinomas, the initial rise in serum Hp coincided closely with the first appearance of a palpable mass. These findings indicate that serum Hp levels in animals with DMBA-induced tumors are related to tumor type. In the absence of hemolytic or nonmalignant inflammatory conditions, the Hp response to a tumor may be a reflection of its inflammatory characteristics. (18 refs)

79-0264 Transmaternal Modification of the Berenblum/Mottram Experiment in Mice. (Eng) Schweizer, J. (Inst. Experimental Pathology, German Cancer Res. Center, In Neuenheimer Feld 280, 6900 Heidelberg, W. Germany); Loehrke, H.; Goertler, K. *Bull Cancer (Paris)* 65(3): 265-270; 1978.

In a modification of the classic two stage initiation-promotion (I-P) carcinogenesis experiment, NMRI mice experienced a significantly greater number of tumors when treated topically 2x/wk for 24 wk with 10 nanomoles 12-O-tetradecanoylphorbol-13-acetate (TPA) after in utero initiation with 7,12-dimethylbenz(a)anthracene (DMBA) given intragastrically to the pregnant mothers. Six groups of mothers received DMBA in 60-150 mg/kg total doses divided into four or five parts over 3- or 4-day periods between days 14 and 21 of gestation. There were 17 abortions in 49 treated mice, but the total number of offspring in treatment and control groups was only slightly different, and all surviving offspring were originally tumor free. Fibroepitheliomas began appearing in all I-P groups 5-9 wk after TPA treatment, and the number of tumor bearing animals increased over time. No papillomas were noted in noninitiated or initiated but not promoted animals over the duration of the experiment. Initiation at 14-18 days of gestation produced the lowest percentage of animals with tumors, initiation at 16-19 days the highest percentage, and later initiation led to a gradual decrease in tumor-bearing animals. The number of tumors/animal followed a similar distribution with respect to time of in utero treatment. Thirty-five animals receiving a total of 60 mg TPA in four doses between days 16 and 19 developed a total of 43 malignant and 55 benign tumors not only of the skin but of lung,

liver, ovaries, mammary glands, vagina, lymph nodes, thymus, and the blood cell system. It is suggested that these findings have direct implications for maternal exposure to subthreshold doses of carcinogen in human pregnancy. (10 refs)

79-0265 Characteristics of Chemically Transformed Mouse Epidermal Cells In Vitro and In Vivo.

(Eng) Fusenig, N. E. (German Cancer Res. Center, Im Neuenheimer Feld 280, D 6900 Heidelberg, W. Germany); Amer, S. M.; Boukamp, P.; Worst, P. K. *Bull Cancer (Paris)* 65(3): 241-247; 1978.

Primary cultures of epidermal cells from newborn mouse skin proliferated and expressed typical epidermal functions for a limited time in vitro. The cultured cells had the features of keratinizing cells, and they exhibited strong reactivity with an epidermis-specific membrane antiserum. These cells were transformed by dimethylbenz(a)anthracene (DMBA) in standard cultures or, more easily, in cultures using 3T3 feeder cells. The transformed cells had an increased proliferation rate, did not pile up or form multilayered cultures like their normal counterparts, and exhibited less keratinization. When the transformed cells were grown in air on collagen gels, they formed irregular clumps with central (horn-pearl) keratinization, whereas normal controls formed stratified structures. The transformed cells exhibited reduced reactivity with tissue-specific membrane antiserum: there was masking or rearrangement of the membrane antigens, with simultaneous exposure of new fetallike antigens. Their reactivity with histocompatibility antisera was reduced only slightly. These cells had both numerical and structural chromosome aberrations. They grew in soft agar, and they induced tumors upon sc injection in syngeneic or allogeneic hosts. When transplanted as cultures (on collagen) or as suspensions, the transformed cells formed epithelial cell cords that invaded the underlying mesenchyme. This growth behavior was typical of an invasive carcinoma. Cell cultures derived from in vivo DMBA-induced tumors behaved like in vitro carcinogen-transformed cells. (27 refs)

79-0266 Effect of Neonatal Administration of Sex Steroids on 7,12-Dimethylbenz(a)anthracene-induced Mammary Carcinoma and Dysplasia in Female Sprague-Dawley Rats. (Eng) Yoshida, H. (First Dept. Pathology, Sch. Medicine, Ehime Univ., Shizukawa, Shigenobu-cho, Onsen-Gun, Ehime-ken 791-02, Japan); Fukunishi, R. *Gann* 69(5): 627-631; 1978.

The effect of neonatal administration of various sex steroids to female Sprague-Dawley rats on the induction of 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary carcinoma and dysplasia was examined. Two-day-old rats were inoculated sc with 1.25 mg testosterone propionate (TSP), 1.0 mg 5 α -dihydrotestosterone (DHT), 0.1 mg 17 β -estradiol

(ED), or 1.0 mg progesterone (PG). All rats were given 20 mg DMBA via stomach tube at 50 days of age and then sacrificed at 300 days of age. In TSP- or ED-treated rats, lactation in the mammary gland and an absence of corpora lutea were found. The induction of mammary carcinoma was strongly suppressed, but the induction of mammary dysplasia was significantly accelerated in these rats. DHT and PG had no effect on the induction of mammary carcinoma or dysplasia. The absence of corpora lutea in the ovaries or a PG deficiency might have played an important role in the suppression of mammary carcinogenesis. (25 refs)

79-0267 Cytochrome P-450 in a Cultured Human Lymphocyte Cell Line. (Eng) Gurtoo, H. L. (Dept. Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY, 14263); Marinello, A. J.; Freedman, H. J.; Paigen, B.; Minowada, J. *Biochem Pharmacol* 27(22): 2659-2662; 1978.

Aryl hydrocarbon hydroxylase (AHH) activity and inducibility were studied in a cultured human lymphocyte cell line, RPMI-1788. The cells were incubated for 48 hr before addition of one of the following AHH inducers: dibenzanthracene (DBA: 0.3 μ M), benzantracene (10.0 μ M), 3-methylcholanthrene (MC: 1.0 μ M), or 2,3,7,8-tetrachlorodibenzo-p-dioxin (0.3 nM). AHH activity, measured 24 hr later, had increased 160%-350% over control values. The difference spectra of microsomes isolated from DBA-induced RPMI-1788 cells and from the liver of rats pretreated with phenobarbital (PB) and MC were compared. As in previous reports, difference spectral maxima of liver microsomes from PB- and MC-treated rats were at 450 and 448 nanometers (nm), respectively. The difference spectral max of the RPMI-1788 cell microsomes was at 451 nm. The spectral examination reveals, therefore, that the mixed-function oxygenase-linked cytochrome in RPMI-1788 is distinct from that in rodents. It is suggested that mechanistic, physical, and biochemical information obtained from studies with rodent liver cytochromes P-450 may not be directly applicable to humans. (14 refs)

79-0268 The Effect of Dinitrochlorobenzene (DNCB) on Dimethylbenzanthracene (DMBA) Carcinogenesis on Hamster Buccal Pouch. (Eng) Murphy, J. B. (Dept. Oral Pathology, Tufts Univ. Sch. Dental Medicine, One Kneeland St., Boston, MA, 02111); Giunta, J. L. *Oral Surg* 46(5): 669-675; 1978.

The effect of dinitrochlorobenzene (DNCB) on dimethylbenzanthracene (DMBA)-induced carcinogenesis of the Syrian hamster buccal pouch was studied. Hamsters were treated with 2% DNCB (applied topically 2x/wk for 2 wk) followed by 0.5% DMBA (applied topically 3x/wk for 10 wk). Controls were treated with DNCB alone or DMBA alone. The histologic characteristics and latent periods of the epidermoid

carcinomas induced by DMBA were not altered by prior treatment with DNCB. However, there was a sensitization of the buccal pouch in animals painted with DNCB, with both gross and histologic evidence of a delayed sensitivity reaction being demonstrated. The data suggest that the cellular response against tumor cells is dependent on specific tumor antigens that are probably very weak in this chemical carcinogenesis system. (11 refs)

- 79-0269** **Mutagenesis and Cell Transformation of Mammalian Cells in Culture by Chemical Carcinogens.** (Eng) Huberman, E. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830). *J Environ Pathol Toxicol* 2(1): 29-42; 1978.

The relationship between mutagenesis and carcinogenicity was studied by testing a series of 11 polycyclic hydrocarbons with different degrees of carcinogenicity in a cell-mediated mutagenesis assay for the induction of ouabain-resistant mutants. Four carcinogens [7,12-dimethylbenz(a)anthracene benzo(a)pyrene (BP), 3-methylcholanthrene and 7-methylbenz(a)anthracene] induced ouabain-resistant mutants, whereas five noncarcinogens were not mutagenic. The 7,8-diol-9,10-epoxide of BP was identified as its major mutagenic and cell-transforming metabolite. Based on the finding that the same metabolites are responsible for cell transformation and mutagenesis in mammalian cells, it was possible to estimate the genetic target size for transformation. This was done by comparing in the same cells (normal golden hamster embryo cells) the frequency of cell transformation and mutation for ouabain resistance (presumably due to mutation at one locus) induced by BP and its (\pm)-trans-7,8-diol. The ratio between cell transformation and mutagenesis for ouabain resistance induced by either hydrocarbon was 20:1, indicating that the target size for transformation is 20 times larger than that determined for ouabain resistance. Therefore, cell transformation may be due to a mutation and this mutation may occur in one out of a small number of the same or different genes. (65 refs)

- 79-0270** **Role of Functional Activity of Connective Tissue in Chemical Carcinogenesis of the Mammary Gland.** (Ukr) Turkevich, N. M. (Inst. Problems Oncology, Kiev, USSR); Vasnetsova, S. S.; Gutnik, N. S.; Matveichuk, Ia. D. *Dopov Akad Nauk Ukr RSR B* (9): 847-849; 1978.

The role of decreased functional activity of the connective tissue caused by various endocrine disorders on the development of 7,12-dimethylbenz(a)anthracene (DMBA)-induced tumors of the mammary glands was evaluated. Random-bred albino rats were inoculated iv with 6 mg DMBA. The animals were then divided into three groups: Group 1 rats underwent transplantation of a homologous hypophysis 2 wk after DMBA exposure; Group 2 rats underwent ovariectomy 25

days after exposure; Group 3 rats underwent sham ovariectomy. Breast tumors were detected in 31/45 rats in Group 1, 0/27 rats in Group 2, and 13/31 rats in Group 3; the av latent period of tumor development in Groups 1 and 3 was 51 and 49 days, respectively. (5 refs)

- 79-0271** **Stimulation of DNA Synthesis by Tumour Promoter and Pure Mitogenic Factors.** (Eng) Dick-er, P. (Imperial Cancer Res. Fund Labs., Lincoln's Inn Fields, London WC2, England); Rozengurt, E. *Nature* 276(5689): 723-726; 1978.

Studies were carried out in mouse and human fibroblast cultures to determine the significance of the serum dependence of the growth-stimulating activity of 12-O-tetradecanoylphorbol-13-acetate (TPA). In synthetic, serum-free medium, TPA interacted synergistically with insulin, epidermal growth factor (EGF), and fibroblast-derived growth factor (FDGF) in stimulating ^3H -thymidine incorporation into acid-precipitable material by quiescent cultures of mouse 3T3 cells. EGF and TPA reproducibly increased DNA synthesis considerably in eight independent experiments, although the magnitude of the increase varied. In the presence of a fixed concentration of insulin, TPA stimulated DNA synthesis in a dose-dependent manner. The lowest concentration of TPA needed to show synergism consistently with 1 $\mu\text{g}/\text{ml}$ of insulin was 5 nanograms/mg. Only 20 min of exposure to the promoter was sufficient to render the cultures sensitive to the mitogenic effect of insulin, EGF, or FDGF. The results indicate that there is a striking synergistic interaction between TPA and growth factors in stimulating DNA synthesis in quiescent cultures of mouse and human fibroblasts maintained in serum-free medium. The possibility that promotion in vivo can be induced by an interaction between the promoter and growth factors should receive serious consideration. (16 refs)

- 79-0272** **Catabolism of 2-Deoxyglucose by Phagocytic Leukocytes in the Presence of 12-O-Tetradecanoyl Phorbol-13-acetate.** (Eng) Zabos, P. (Dept. Pediatrics, Mount Sinai Medical Center, 1 Gustave L. Levy Place, New York, NY, 10029); Kyner, D.; Mendelsohn, N.; Schreiber, C.; Waxman, S.; Christman, J.; Acs, G. *Proc Natl Acad Sci USA* 75(11): 5422-5426; 1978.

Data indicating that 12-O-tetradecanoylphorbol-13-acetate (TPA) dramatically increases the rate of decarboxylation of 2-deoxyglucose (2-dGlc) by granulocytes, monocytes, and macrophages are presented. In the presence of 10 nanograms/ml TPA, human granulocytes, monocytes, mouse macrophages, and HL-60 cells (a line established from a patient with acute myeloid leukemia) released greatly increased amounts of carbon-1 (as $^{14}\text{CO}_2$) from ^{14}C -labeled 2-dGlc and glucose. These cells released barely detectable amounts of CO_2 in the absence of TPA. In contrast, T lymphocytes, B lym-

phocytes, RBC, and platelets released low levels of CO₂ in both the presence and absence of TPA. In the granulocytes, there was concurrent intracellular accumulation of a phosphorylated 5-carbon intermediate. Chromatographic analysis of the intracellular pool revealed the presence of 2-dGlc 6-phosphate, 2-deoxygluconic acid 6-phosphate, and the phosphorylated compound, which reacted with phenylhydrazine. This finding suggests that the mechanism of 2-Glc catabolism in the presence of TPA is analogous to the catabolism of glucose via the hexose monophosphate shunt. Several lines of evidence indicate that enzymes of this shunt are able to mediate the oxidative decarboxylation of 2-dGlc. Phorbol didecanoate, which also possesses inflammatory and tumor-promoting activity, and mezerein, which resembles TPA in its ability to inhibit cell differentiation and enhance plasminogen activator production, also increased CO₂ release. (28 refs)

- 79-0273 Hepatic Mixed-Function Oxidase Activity in Rainbow Trout Exposed to Several Polycyclic Aromatic Compounds.** (Eng) Gerhart, E. H. (Dept. Chemistry, Univ. Minnesota, Duluth, MN, 55812); Carlson, R. M. *Environ Res* 17(2): 284-295; 1978.

The effects of polycyclic aromatic hydrocarbons (PAH) on microsomal liver enzymes were examined in rainbow trout. Various PAH were injected ip to screen for mixed-function oxidase (MFO) activity. Chrysene, benzo(a)pyrene (BP), and Aroclor 1254 induced MFO activity. When fish were also exposed to solubilized pyrene, fluoranthene, and BP in water, a bioaccumulation of BP resulted in MFO induction, whereas a bioaccumulation of pyrene and fluoranthene did not. Based on the results of water and injection exposure to BP, it was predicted that tissue concentrations in excess of 300 µg/kg BP would be accompanied by MFO induction in rainbow trout. (36 refs)

- 79-0274 Effect of Selective T Cell Depletion in Modulating the Behaviour of Fibrosarcomas in Mice.** (Eng) Gupta, S. (Dept. Pathology, Postgraduate Inst. Medical Education and Res., Chandigarh-160012, India); Sehgal, S.; Aikat, B. K. *Indian J Med Res* 68: 300-305; 1978.

The role of selective T-cell depletion in inducing metastases of methylcholanthrene (MCA)-induced fibrosarcomas was studied in C57 mice. T-cell depleted mice were produced by thymectomy at 3 wk, followed by 850 R of irradiation and repopulation with 2 x 10⁶ cells from syngeneic bone marrow. Sc injection of 10⁶ MAC-induced fibrosarcoma cells induced a large localized tumor in normal animals within 10 days with no visceral metastases; 2/15 animals showed metastases in the axillary nodes. In the T-cell depleted mice, injection of 10⁶ fibrosarcoma cells induced 13 metastases in 7/15 animals, ie, in the lung (5), axillary node (4), right inguinal lymph node (2), and peritoneal cavity (2). There was no significant differ-

ence in the latent period or in tumor size between the T-cell depleted and control animals. It is concluded that a significant proportion of T-cell depletion favors the development of visceral metastases in C57 mice, while such metastases are not found in fully immunocompetent animals. (24 refs)

- 79-0275 Induction of Aryl Hydrocarbon Hydroxylase by 3-Methylcholanthrene in Liver, Lung and Kidney of Gonadectomized and Sham-operated Wistar Rats.** (Eng) Warren, P. M. (Div. Pharmacology and Toxicology, Faculty Pharmaceutical Sciences, Univ. British Columbia, Vancouver, B.C., V6T 1W5, Canada); Bellward, G. D. *Biochem Pharmacol* 27(21): 2537-2541; 1978.

Dose-response curves were obtained for the induction of aryl hydrocarbon hydroxylase (AHH), measured as benzpyrene hydroxylase, in liver, lung, and kidney by the administration of methylcholanthrene (MC; 0-40 mg/kg ip) in Wistar rats. Lung was the tissue most sensitive to induction, followed by liver and then kidney. Although liver exhibited the greatest overall activity, the percent increase over control AHH levels was much higher in the two extrahepatic tissues. There were no significant differences in the AHH activities of sham and ovariectomized females in any of the tissues at the control levels or after MC treatment. However, castration of the males decreased liver enzyme levels and increased kidney enzyme levels in controls. The AHH levels achieved after maximal MC induction were the same in the livers of castrated and in sham-operated male rats. Significantly increased maximal induction was observed in the kidney following MC administration in castrated males. These results indicate that local effects of toxic metabolites formed in such areas as the lung are likely to be of importance in tumor induction. (38 refs)

- 79-0276 Influence of Transplacental 3-Methylcholanthrene on Aryl Hydrocarbon Hydroxylase Activity of Mouse Lung.** (Eng) Hunt, W. G. (Dept. Pharmacology, Univ. Vermont, Burlington, VT); Knight, S. E.; Soyka, L. F. In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 999-1014; 1977.

To determine whether perinatal exposure to 3-methylcholanthrene (3-MC) produces changes in the lung's ability to metabolize or detoxify polycyclic hydrocarbons, pregnant outbred Swiss-Webster mice were treated with 4 mg 3-MC in oil sc on 2 successive days prior to delivery. Lung aryl hydrocarbon hydroxylase (AHH) activity in the offspring was studied as a function of age, sex, strain, and inducibility. Lung AHH peaked at a higher level and decreased more rapidly with age in males than in females. AHH activity was four

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times higher in 10-day-old treated male and female offspring than in controls, but at 20 days this difference was no longer statistically significant. The magnitude of the responses to induction by 3-MC pretreatment (300%-600%) did not differ significantly from controls, compared with 3-MC-exposed mice of either sex. In studies of strain differences, basal AHH levels at 20 days of age were lower for (DBA/1J x SWR) F_1 mice than for Swiss-Webster, C57BL/6J, and (C57BL/6J x C3H/HeJ) F_1 mice. Females had higher basal levels than males at 10 wk in the SWR/J and (C57BL/6J x C3H/HeJ) F_1 strains and lower levels than males in the C57BL/6J mice. The induction ratio was greater for all strains in the 10-wk-old mice than for neonates, although absolute levels at these two ages were identical. Foster studies showed that lung AHH levels were elevated to a greater extent by exposure to 3-MC and its metabolite in the milk than via the transplacental route. Pre- and/or postnatal exposure to carcinogens could influence the manner in which adults respond to reexposure to the same or related compounds. (16 refs)

- 79-0277 Time Course of the Induction of Aryl Hydrocarbon Hydroxylase in Rat Liver Nuclei and Mitochondria by Phenobarbital, 3-Methylcholanthrene, 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, Dieldrin and Other Inducers.** (Eng) Viviani, A. (Inst. Toxicology, Federal Inst. Technology, CH-8603 Scherzenbach, Switzerland); Lutz, W. K.; Schlatter, C. *Biochem Pharmacol* 27(17): 2103-2108; 1978.

The time course of the induction of aryl hydrocarbon hydroxylase (AHH) was measured in male liver nuclei and mitochondria after treatment of adult animals (Sprague-Dawley-derived SIV 50 strain) with various inducers for up to 14 days. After daily ip injection of 3-methylcholanthrene (MC, 20 mg/kg), the nuclear activity increased to a max of 600% of the control activity after 4 days, whereas the mitochondrial activity was 400% of the control activity at the same date. After 12 days, both activities equilibrated at 400%. A similar time course was found after a single ip injection of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (0.01 mg/kg) with an induction of 500% and 300% for nuclei and mitochondria, respectively, after 2 days, and to 400% for both after 12 days. Phenobarbital (PB) was given continuously in the drinking water (1 g/liter); it induced mitochondrial activity to 200% after 8 days and 170% after 14 days. The nuclear activity was only slightly induced to a constant level of 130% between days 8 and 14. Dieldrin did not significantly increase the mitochondrial activity after daily ip injection (20 mg/kg), but the nuclear activity was raised to 200% after 3 days, and lowered to control values after 12 days. Other inducers tested were benz[a]anthracene (BA), hexachlorobenzene (HCB), and 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT). The induction pattern with BA was similar to that of MC, a model compound for the group of cytochrome P-448 inducers. The induction by HCB and DDT resembled that by PB, a typical cytochrome P-450 inducer. The results indicate that long-term treatment results in an equal relative induction of

AHH activity in mitochondria and nuclei and that only the absolute value of the induction is dependent on the inducer used. (29 refs)

- 79-0278 The Influence of Phenobarbital, 3-Methylcholanthrene, and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Glutathione S-Transferase Activity of Rat Liver Cytosol.** (Eng) Baars, A. J. (Dept. Pharmacology, Univ. Leiden, Subfaculty Pharmacy, Sylvius Labs., Wassenaarseweg 72, Leiden, Netherlands); Jansen, M.; Breimer, D. D. *Biochem Pharmacol* 27(21): 2487-2494; 1978.

The influence of the drug-metabolizing enzyme inducers, phenobarbital (PB), 3-methylcholanthrene (MC), and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) on glutathione (GSH) S-transferase activity in rat liver cytosol was studied using styrene oxide (STOX), 1,2-butylene oxide (BOX), and 1-chloro-2,4-dinitrobenzene (CDNB) as the electrophilic substrates. Assuming Michaelis-Menten kinetics, apparent K_m and V_{max} values of the GSH S-transferase activities were calculated using a computer program. Pretreatment of the rats with MC (20 mg/kg ip 1x/day for 4 days) resulted in enhancement of all measured activities expressed in terms of cytosol protein, while TCDD administration (10 μ g/kg ip 1x/day on days 1 and 7) enhanced only the activities expressed on a per gram body wt basis. PB administration (80 mg/kg ip 1x/day for 14 days) enhanced activities by both standards when STOX was the substrate, but when CDNB was the substrate, only the activity per gram body wt increased. All pretreatments increased the V_{max} values when CDNB was the substrate, while PB and MC had enhancing effects when STOX was the substrate. The V_{max} with BOX as substrate was enhanced only after TCDD administration. The K_m values when BOX was the substrate were lowered after MC pretreatment. TCDD pretreatment decreased the K_m for the STOX substrate, while it increased the K_m for the CDNB substrate. It is concluded that the GSH S-transferase system is inducible. Qualitative differences were not observed between the inducing effects of PB and MC; however, TCDD administration resulted in a different induction pattern, which may indicate that induction with this latter agent involves different forms of GSH S-transferases. (42 refs)

- 79-0279 Effect of Typical Inducers of Microsomal Drug-Metabolizing Enzymes on Phospholipid Metabolism in Rat Liver.** (Eng) Ishidate, K. (Medical Res. Inst., Tokyo Medical and Dental Univ., Kanda-Surugadai, Chiyoda-ku, Tokyo 101, Japan); Yoshida, M.; Nakazawa, Y. *Biochem Pharmacol* 27(22): 2595-2603; 1978.

The effect of pretreatment with phenobarbital (PB; 80 mg/kg/day po), polychlorinated biphenyls (PCB; 100 mg/kg/day po), and 3-methylcholanthrene (3-MC; 50 mg/kg/day ip) on the metabolism of phospholipids in liver was studied in male Wistar rats. PB, PCB, or 3-MC was given

on two successive days. On the third day, animals were injected ip with (^{32}P)orthophosphate (200-250 μCi) or ($\text{Me-}^{14}\text{C}$)choline chloride (3.8 μCi) and killed 1 hr later. PB had no significant effect on the incorporation of ^{32}P into liver microsomal phospholipid but the rate of incorporation of (^{14}C) choline into phosphatidylcholine (PC) in both subcellular components of the liver and blood plasma decreased slightly. The ratio of (^{14}C) specific activity of phosphorylcholine to that of microsomal phospholipid was considerably higher in PB-treated rats compared with the ratio in control rats. These and previous findings suggest that proliferation of liver endoplasmic reticulum membranes induced by PB would be accompanied by the stimulation of phospholipid synthesis at early times followed by a decrease in the turnover rate of microsomal phospholipids. The administration of PCBs caused strong inhibition of both ^{32}P and ^{14}C incorporation into PC in liver subcellular fractions. The secretion of PC from liver cells into blood plasma was also strongly depressed as was phospholipid catabolizing activity in the liver. The decrease in ^{32}P incorporation into liver microsomal PC was also observed in rats treated with 3-MC. The mechanism of the observed inhibitions remains to be elucidated. (54 refs)

79-0280 Model Quantum-Chemical Studies on the Reaction Between the Candidate Proximate Carcinogen Benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide and Guanine. (Eng) Lavery, R. (Institut de Biologie Physico-Chimique, Laboratoire de Biochimie Theorique associe au C.N.R.S., 13, rue P. et M. Curie, 75005 Paris, France); Pullman, A.; Pullman, B. *Int J Quant Chem Quant Biol Symp* (5): 21-34; 1978.

A model involving "bay-region" diol epoxides as possible proximate metabolites for polycyclic aromatic hydrocarbons that form adducts with the bases of cellular nucleic acids is presented. The mechanism by which these adducts are formed is hypothesized to consist of an electrophilic substitution on the NH_2 group of guanine by a carbonium ion derived from the opening of an epoxide. It involves the formation of a quaternary intermediate followed by hydroxyl-assisted deprotonation. (19 refs)

79-0281 Mutagenicity of Optically Pure (-)trans-7,8-Dihydroxydihydrobenzo(a)pyrene. (Eng) Nagao, M. (Biochemistry Div., Natl. Cancer Center Res. Inst., Tsukuba, Chuo-ku, Tokyo 104, Japan); Sugimura, T.; Yang, S. K.; Gelboin, H. V. *Mutat Res* 58(2/3): 361-365; 1978.

The mutagenicity of the (+) and (-) enantiomers of trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene (trans-7,8-diol), their di(-)methoxyacetates, and the hydrolysis and reduction products of two diol-epoxide derivatives of benzo(a)pyrene (BP) were tested using *Salmonella typhimurium* strains TA100 and TA98 with and without rat liver microso-

mal activation. The (-)trans-7,8-diol was strongly mutagenic to TA100 in the absence of microsomal activation while the (+)trans-7,8-diol was weakly mutagenic. Microsomal activation enhanced the number of revertants in TA100 1.5-fold at doses of 4-6 $\mu\text{g}/\text{plate}$ with the (-)trans-7,8-diol. The (-)trans-7,8-diol was not mutagenic to TA98 in the absence of the microsomal preparation but weakly mutagenic with activation. With activation, the (+)enantiomer was a much stronger mutagen in TA98 than was the (-)enantiomer. The di(-)methoxyacetates of both (+)- and (-)-trans-7,8-diols were not mutagenic to TA100 or TA98 with or without activation. Of the hydrolysis and reduction products of the diol-epoxide derivatives tested, the (7/8,9)-triol and (7,9/8) triol were very weakly mutagenic to TA100 with activation. None of the tetrols was mutagenic to TA100 or TA98 with or without activation. These results suggest that the (-)trans-7,8-diol and the (+)trans-7,8-diol can exhibit mutagenic activity with microsomal activation. The (-)trans-7,8-diol may be a direct mutagen. (16 refs)

79-0282 Antioxidants and the Mutagenicity of Benzo(a)pyrene and Some Derivatives. (Eng) Calle, L. M. (Dept. Chemistry, Ohio Univ., Athens, OH, 45701); Sullivan, P. D.; Nettleman, M. D.; Ocasio, I. J.; Blazyk, J.; Jollick, J. *Biochem Biophys Res Commun* 85(1): 351-356; 1978.

The effects of antioxidants on the mutagenicity of benzo(a)pyrene (BP), 6-methylbenzo(a)pyrene (6-MeBP), and 10-methylbenzo(a)pyrene toward *Salmonella typhimurium* strain TA98 were determined. In the Ames mutagenicity assay, 6-MeBP and 10-MeBP were approx six and two times more mutagenic than BP, but 6-methoxybenzo(a)pyrene and 7,10-dimethylbenzo(a)pyrene were considerably less active than BP. The antioxidants phenazine methosulfate, phenothiazine, 2,3,6,7-tetramethoxythianthrene, ethoxyquin, 4-hydroxy-2,2,6,6-tetramethylpiperidinoxy, Irganox 1010, 3,3',5,5'-tetra-*t*-butyl-4,4'-biphenol, Ethyl 736, butylated hydroxytoluene, and butylated hydroxyanisole inhibited mutagenic capabilities when added at antioxidant/hydrocarbon ratios of approx 10, 60, and 20 for BP, 6-MeBP, and 10-MeBP, respectively. (31 refs)

79-0283 Electric Linear Dichroism Study on the Orientation of Benzo[a]pyrene-7,8-dihydrodiol 9,10-Oxide Covalently Bound to DNA. (Eng) Geacintov, N. E. (Dept. Chemistry, Radiation and Solid State Lab., New York Univ., New York, NY, 10003); Gagliano, A.; Ivanovic, V.; Weinstein, I. B. *Biochemistry* 17(24): 5256-5262; 1978.

The electric linear dichroism spectra of native calf thymus DNA modified to a small extent by reaction with (\pm)-7 β ,8 α -dihydroxy-9 α ,10 α -epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (BPDE) were measured, as were the spectra of physical complexes of benzo(a)pyrene (BP) and proflavine (PF) with DNA. The linear dichroism δA of the covalent BPDE-DNA

complex in the wavelength region of the absorption of the pyrenelike BPDE chromophore was positive. In contrast, δA was negative in the absorption region of the DNA bases, as well as in the absorption region of the BP and PF molecules physically bound to DNA. It is concluded that the orientation of the BPDE moiety is not of the intercalation type, as is the case for the physical BP and PF complexes. The reduced linear dichroism was wavelength dependent for the BPDE-DNA and BP-DNA complexes, which indicated that there is a heterogeneity of binding sites with different orientations. There appears to be one major type of oriented BPDE covalently bound to DNA. The long axis of the pyrenelike chromophore of BPDE lies on the surface of a cone whose axis is that of the DNA helix and whose angle, with respect to this axis, is ≤ 35 degrees. The planes of BP and PF were nearly parallel to the planes of the DNA bases. (27 refs)

79-0284 Polycyclic Hydrocarbon-induced Rat Sarcomas Correlated to Disturbances in the Deoxyadenylate Regions of the Tumor DNAs. (Eng) Pero, R. W. (Dept. Nucleic Acid Biochemistry, Lund Univ., Wallenberg Lab., Fack 7031, 220 07 Lund, Sweden); Bryngelsson, T.; Rudnick, C.; Levan, G. *Eur J Cancer* 14(9): 961-969; 1978.

An attempt was made to correlate polycyclic hydrocarbon-induced rat sarcomas to disturbances in the deoxyadenylate regions of the tumor DNA's. Inbred Wistar-Furth rats (8-35 days of age) were inoculated sc with 1- to 4-mg doses of benzo(a)pyrene (BP), 20-methylcholanthrene (MC), or 7,12-dimethylbenz(a)anthracene (DMBA). Tumors developed to a 100% incidence, and they were harvested 6-8 wk after they were palpable (< 7 mo). Ten separate tumor groups containing a total of 51 rat sarcomas were examined for agent-related abnormalities in their DNA's. The levels of deoxyadenylate (dA) regions in normal and tumor rat DNA's were estimated by annealing ^3H -polyuridylic acid to DNA and treating the resultant hybrids with ribonuclease A. All the tumor material had significant reductions in the dA regions of their DNA's when the levels were compared with normal rat DNA. Although the dA reductions were heterogeneous from one tumor group to the other, irrespective of the inducing agent, the greatest decreases tended to occur with tumors induced by MC and DMBA. No relationship was found between dA alterations and types of chromosomal aberrations in the tumor cell populations. However, normal and tumor DNAs, fractionated into adenine + thymine (A + T)-rich and guanine + cytosine (G + C)-rich DNA by thermal elution from hydroxyapatite columns, showed specific neoplastic-associated dA disturbances in the A + T-rich DNA of tumors induced by BP, MC, and DMBA. The base compositions of the tumor material were also analyzed and compared with normal rat DNA. Tumors induced by DMBA showed highly significant decreases in percent A + T, whereas BP- and MC-induced tumors tended to show only small increase in percent A + T. Some tumors induced by BP, MC, and DMBA were unaltered in base composition. The results are consistent with the hypothesis that DMBA is the strong-

est carcinogen in the series because it interacts preferentially with A + T-rich DNA, which is the type of DNA most important for polycyclic hydrocarbon-induced neoplasms in the rat. (31 refs)

79-0285 Effect of Benzene and Benzo(a)pyrene on Protein Synthesis in Isolated Nuclei and Chloroplasts. (Rus) Durmishidze, S. V. (Inst. Plant Biochemistry, Tbilisi, USSR); Dzhokhadze, D. I. *Dokl Akad Nauk SSSR* 242(2): 453-456; 1978.

The effect of benzene and benzo(a)pyrene (BP) on protein synthesis was studied in nuclei isolated from rat liver, and in nuclei and chloroplasts isolated from the leaves of 7- to 9-day-old pea plants. The intensity of protein synthesis was measured by the rate of ^{14}C -leucine incorporation. Incubation of the samples with benzene (at a ratio of 25 μl /50-100 μg DNA) resulted in stimulation of protein synthesis by 9%-31%. BP-induced stimulation of protein synthesis in leaf and liver nuclei was observed at a ratio of 3-4.5 μg BP/100 μg DNA and 1.5-3.0 μg BP/100 μg DNA, respectively (by 5%-27% and 3%-28%, respectively); in the chloroplasts, a stimulation of protein synthesis by 12%-27% was observed at a ratio of 1.5 μg BP/100 μg DNA. (13 refs)

79-0286 DNA-Carcinogen Interactions. (Eng) Dipple, A. (NCI, Frederick Cancer Res. Center, Frederick, MD, 21501); Baird, W. M.; Bigger, C. A.; Moschel, R. C.; Andrews, A. W. In: *Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second Food and Drug Administration Office of Science Summer Symposium held in Annapolis, 31 August-2 September 1977*. Office of Science, FDA (Annapolis, MD) HEW Publication No. (FDA)78-1046: 241 pp.; 4-7; 1978.

Chemical analysis of products of the reaction between carcinogenic polycyclic hydrocarbons and DNA has elucidated the mechanisms involved in the activation of two such carcinogens, benzo(a)pyrene and 7,12-dimethylbenz(a)anthracene (DMBA). Whereas structure-activity studies had focused attention on the K-region oxides of these compounds with misleading results, chemical analysis revealed that the metabolites of carcinogenic importance were the diol-epoxides. The binding of DMBA to DNA was studied in *Salmonella* in the presence of a rat liver S-9 or microsomal fraction. However, reproducible nucleoside-DMBA adducts from the *Salmonella* DNA were not obtained. DMBA-DNA binding has also been studied in mouse embryo cells and in mouse skin in vivo. Chromatograms of the adducts from the mouse embryo cells and from the mouse skin in vivo are essentially superimposable. In the *Salmonella*/microsomal system, the results indicated that the K-region oxide of DMBA is generated and that it is responsible for binding to DNA. Thus, the activation systems used in bacterial muta-

genesis assays may not faithfully reproduce the activation processes that occur in mammalian tissues. (14 refs)

- 79-0287** Survey of Food Contamination by Benzo(a)pyrene. II. Study of Smoked Products. (Fre) Bories, G. (Laboratoire de recherches sur les additifs alimentaires, I.N.R.A., 180 chemin de Tournefeuille, 31300 Toulouse, France); Tchimbakala, A.; Tchimbakala, E. *Ann Nutr Aliment* 32(4): 811-817; 1978.

Smoked meat, poultry, and fish were analyzed for benzo(a)pyrene residues. The residue levels were $<0.5 \mu\text{g/kg}$ in most samples and $<1 \mu\text{g/kg}$ in all samples except anchovies, in which up to $7 \mu\text{g/kg}$ were found. (12 refs)

- 79-0288** Fibrosarcoma Induced by Administration of Methyl Cholanthere into Post Extraction Sockets of Mandibular Molars in Rats. (Eng) Sela, J. (Div. Oral Pathology, Hebrew University-Hadassah, Sch. Dental Medicine, P.O. Box 1172, Jerusalem, Israel); Harary, D. *Experientia* 35(1): 110-111; 1979.

The effect of 20-methylcholanthere (20-MC) on the tissues involved in the healing of alveolar bone sockets was studied using 55 male and female Hebrew University rats. Following extraction of the mandibular first and second right molars, 10% 20-MC in pellet or crystalline form was introduced into the alveolar bone sockets. In addition, 10% 20-MC in vitepsol H-15 was injected into the surgical site 20 days postsurgery (30 rats) or on 10, 20, and 30 days postsurgery (25 rats). The animals were observed for 9 mo. Fibrosarcomas developed in all surviving 20-MC-treated rats, but osteosarcomas were not induced. These methods are highly recommended for the production of experimental fibrosarcomas, but their use for osteosarcoma induction requires further evaluation. (5 refs.)

- 79-0289** The Aftermath of Feeding of Rats with Canned Fish. (Rus) Neiman, I. M. (Inst. Nutrition, Moscow, USSR); Andrianova, M. M.; Beloshapko, A. A.; Gortalum, G. M.; Kolosnitsina, N. V.; Finogenova, M. A. *Vopr Pitan* (5): 60-67; 1978.

A potential hazard of prolonged consumption of canned fish was evaluated in random-bred rats. Animals were divided into four groups: 86 rats in Group 1 were fed with Atlantic herring in tomato sauce, 76 rats in Group 2 with sprats in tomato sauce, 85 rats in Group 3 with sardines in oil, and 70 rats in Group 4 with a standard diet. The experiment lasted 3 yr. At the end of the experiment, tumors were detected in 14.1% of the rats in Group 1 (10.6% had adenocarcinomas and spindle cell liposarcoma of the mammary gland; 3.5% had benign adenomas and fibroadenomas), 23.3% of the rats in Group 2 (20.5% had adenocarcinomas of the

mammary gland, sarcomas of various locations, or cancer of the thyroid, liver, and skin; 2.7% had benign fibroadenomas of the mammary gland), and in 22% of the rats in group 3 (19.5% had sarcomas and adenocarcinomas of the mammary gland, stomach, liver and lungs; 2.4% had benign adenomas of the mammary gland). The incidence of spontaneous malignant and benign tumors in Group 4 was 6% and 10.4%, respectively. The av latent period of tumor development in Groups 2 and 3 rats was 16 mo and 17 mo, respectively, compared with 20 mo in Group 4. With these findings in mind, the cans were analyzed for the presence of benzo(a)pyrene (BP) and dimethylnitrosamine (DMNA). It was found that Atlantic herring contained $0.41 \mu\text{g/kg}$ of BP and $6.0 \mu\text{g/kg}$ of DMNA, sprats contained $0.08 \mu\text{g/kg}$ and $10.0 \mu\text{g/kg}$, respectively, and sardines contained $1.6 \mu\text{g/kg}$ and $15.0 \mu\text{g/kg}$, respectively. (20 refs)

- 79-0290** Survey of Food Contamination by Benzo(a)pyrene. I. Development of a Universal Method of Determination. Its Application to Complete Meals Prepared by Institutional Catering Services. (Fre) Bories, G. (Laboratoire de recherches sur les additifs alimentaires, I.N.R.A., 180 chemin de Tournefeuille, 31300 Toulouse, France); Tchimbakala, A.; Tchimbakala, E. *Ann Nutr Aliment* 32(4): 801-809; 1978.

A universal spectrofluorometric method was developed for the determination of benzo(a)pyrene in food. The sensitivity of the method was 0.2 ppb at a recovery rate of 85%. The benzo(a)pyrene levels found in complete meals prepared by catering services were $0-1 \mu\text{g/kg}$. (11 refs)

- 79-0291** Rapid Method for the Isolation and Quantitative Analysis of Benzo(a)pyrene in Food. (Ger) Gertz, C. (Chemisches Untersuchungsamt der Stadt Hagen, Pappelstrasse 1, D-5800 Hagen, W. Germany). *Z Lebensm Unters Forsch* 167(4): 233-237; 1978.

The presence of benzo(a)pyrene (BP) in foods can be determined quantitatively by thin-layer chromatography and fluorometry. The BP is first extracted from a petroleum-ether suspension of the sample as a water-soluble caffeine complex, reextracted, and then purified by column chromatography. The recovery rate is 80%. (12 refs)

- 79-0292** Marked Differences in the Skin Tumor-initiating Activities of the Optical Enantiomers of the Diastereomeric Benzo(a)pyrene 7,8-Diol-9,10-epoxides. (Eng) Slaga, T. J. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Bracken, W. J.; Gleason, G.; Levin, W.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res* 39(1): 67-71; 1979.

The abilities of the optically pure (+) and (-)-enantiomers of the diastereomeric 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrenes derived from the enantiomeric trans-7,8-dihydrodiols to initiate skin tumors in female Charles River CD-1 mice were determined using a two-stage system of tumorigenesis. (+)-Benzo(a)pyrene (BP) 7 β ,8 α -diol-9 α ,10 α -epoxide 2 (A) effectively initiated tumors in a dose-dependent fashion, whereas (-)-BP 7 β ,8 α -diol-9 β ,10 β -epoxide 1, (-)-BP 7 α ,8 β -diol-9 β ,10 β -epoxide 2 (B), and (+)-BP 7 α ,8 β -diol-9 α ,10 α -epoxide 1 had little or no tumorigenic activity. Compound A had approx 60% of the tumor-initiating activity of BP, compound B approx 2%. Removing the keratinized portion of the skin by pressure-sensitive tape 1 and 2 days before initiation increased the initiating activity of A. In skin tumor-sensitive female Sencar mice, compound A had about 70% of the skin tumor-initiating activity of BP, but the other BP 7,8-diol-9,10-epoxides had little or no tumorigenic activity. Six daily topical applications of 34 nanomoles (nmol) of A resulted in greater tumor-initiating activity than did a single application of 200 nmol, but the activities of BP and B were not increased by fractionated doses. The results indicate that A is the ultimate carcinogenic form of BP 7,8-diol-9,10-epoxide. (30 refs)

79-0293 Tumorigenicity of the Optical Enantiomers of the Diastereomeric Benzo(a)pyrene 7,8-Diol-9,10-epoxides in Newborn Mice: Exceptional Activity of (+)-7 β ,8 α -Dihydroxy-9 α ,10 α -epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene. (Eng) Buening, M. K. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NJ, 07110); Wislocki, P. G.; Levin, W.; Yagi, H.; Thakker, D. R.; Akagi, H.; Koreeda, M.; Jerina, D. M.; Conney, A. H. *Proc Natl Acad Sci USA* 75(11): 5358-5361; 1978.

Benzo(a)pyrene (BP) optical enantiomers were tested for tumorigenicity. The four optically pure isomers of the diastereomeric BP-7,8-diol-9,10 epoxides were tested in newborn Swiss-Webster BLU:Ha(ICR) mice. BP-, (-)-BP-7 β ,8 α -diol-9 β ,10 β -epoxide 1, (+)-BP-7 α ,8 β -diol-9 α ,10 α -epoxide 1, (-)-BP-7 α ,8 β -diol-9 β ,10 β -epoxide 2, and (+)-BP-7 β ,8 α -diol-9 α ,10 α -epoxide 2 were each injected ip into mice in three injections (before 24 hr, at 8 days, and at 15 days of age) to a total dose of 7 nmol or 14 nmol of compound. Upon sacrifice at 34-37 wk, all mice injected with 14 nmol of (+)-BP-7 β ,8 α -diol-9 α ,10 α -epoxide 2 developed pulmonary tumors at a rate of 7.67 tumors/mouse and 71% of those injected with 7 nmol of the compound developed an av of 1.72 tumors/mouse. Only 9%-22% of control mice or mice injected with any dose of the other compounds developed pulmonary tumors (0.09-0.34 tumors/mouse). Because BP is metabolized in vitro with high specificity to (+)-BP-7 β ,8 α -diol-9 α ,10 α -epoxide 2 by liver enzymes and by other target tissues and because it possesses appreciable tumorigenic activity, it is suggested that this compound is a major ultimate carcinogenic metabolite of BP. (39 refs)

79-0294 The Effect of Norharman on the Metabolism of Benzo(a)pyrene by Rat-Liver Microsomes in Vitro in Relation to its Enhancement of the Mutagenicity of Benzo(a)pyrene. (Eng) Fujino, T. (Serology Div., Natl. Cancer Center Res. Inst., 5-1 Tsukiji, Chuo-ku, Tokyo, Japan); Fujiki, H.; Nagao, M.; Yahagi, T.; Seino, Y.; Sugimura, T. *Mutat Res* 58(2/3): 151-158; 1978.

The effect of norharman (NH) on the metabolism of benzo(a)pyrene (BP) by Sprague-Dawley rat liver microsomes was studied. Separation on the metabolites into hydrophilic and hydrophobic fractions showed that NH inhibited the conversion of hydrophobic BP metabolites to hydrophilic ones. Analysis of the hydrophobic metabolites by high-pressure liquid chromatography indicated that NH also inhibited the disappearance of BP itself. However, large amounts of hydrophobic metabolites, such as phenol, quinones and diols, were formed in the presence of NH, and formation of the potent mutagen 7,8-dihydroxyBP was increased tenfold by NH. The increased formation of this compound may be one of the factors responsible for the enhancing effect of NH on the mutagenicity of BP in *Salmonella typhimurium*. (15 refs)

79-0295 The Tumor-producing Effect of Automobile Exhaust Condensate and Fractions Thereof. Part II: Animal Studies. (Eng) Brune, H. (Beratungsfürum für Präventivmedizin und Umwelttoxikologie, Kattrepelsbrücke, 2000 Hamburg 1, W. Germany); Habs, M.; Schmahl, D. *J Environ Pathol and Toxicol* 1(6): 737-745; 1978.

The ability of automobile exhaust condensate and its fractions to produce tumors was studied in mice. In one study, 0.26, 0.79, or 2.37 mg of automobile exhaust condensate or its fractions were applied to the shaved, interscapular region of CFLP mice 3x/wk. The percentage of follicles in which sebaceous glands had disappeared was recorded. In another study, 0.1 ml of each substance was applied 2x/wk for life. The animals were dissected, and both the skin and organs showing abnormalities were examined histologically. In the first study, benzo(a)pyrene, the methanol phase, and cyclohexane phase II were significantly less oncogenic than the total condensate. In the second trial, no significant differences in tumor occurrence could be found between animals treated with fractions containing polycyclic aromatic hydrocarbons (PAH) and those created with the total condensate. (15 refs)

79-0296 The Tumor-producing Effect of Automobile Exhaust Condensate and Fractions Thereof. Part III: Mathematical-Statistical Evaluation of the Test Results. (Eng) Misfeld, J. (Institut für Mathematik, Technische Universität Hannover, Welfengarten 1, 3000 Hannover, W. Germany); Timm, J. *J Environ Pathol and Toxicol* 1(6): 747-771; 1978.

The results of experiments concerning the dose-dependence of carcinogenesis produced by automobile exhaust gas condensate and the condensate fractions responsible for carcinogenesis were evaluated statistically. In particular, the hypothesis that the potency of the entire condensate is mainly due to the fraction containing polycyclic aromatic hydrocarbons (nitromethane phase) was examined. The cyclohexane phase I comprised 34% of the wt of the total condensate, and its relative potency was three times that of the total condensate. The nitromethane phase comprised 17% of the total wt and was approx six times as potent as the total condensate. The remaining part of the cyclohexane phase I (ie, the methanol phase) proved to be responsible for only about 13% of the total potency. Benzo(a)pyrene was responsible for about 10% of the potency of the whole condensate. These results suggest that the nitromethane phase is responsible for a large part of the carcinogenic activity of automobile exhaust condensates. (20 refs)

79-0297 Determination of Chrysene and Benzopyrene in the Atmospheric Environment by Mass Spectrometry. (Jpn) Kuwata, K. (Environmental Pollution Control Center, Osaka, 1-3-62, Nakamichi, Higashinari-ku, Osaka-shi, Japan). *Bunseki Kagaku* 27(10): 650-655; 1978.

A simple, sensitive mass spectrometric method was developed to determine chrysene (CHR) and benzopyrene (BP) in the air. Airborne particulate matter was sampled on a glass fiber filter by a high-volume air sampler for 1 to 24 hr and extracted for 5 hr with 50 ml of cyclohexane in a soxhlet extractor. The extract was reduced to 5 ml by evaporation in a Kuderna-Danish apparatus. Five μ liters of soln was taken into a glass fiber filter sampling probe and 2 μ liters of an internal standard soln containing 100 nanog of benzanthrone (mol wt 234) was added. The sampling probe was dried at room temperature for 2 min and inserted into the ionization chamber of a mass spectrometer. Ion currents of m/e (mass/electric charge) 228, m/e 252, and m/e 234 were measured every 30 sec by the mass spectrometer. Amounts of CHR and BP in the extract were calculated from integrated ion currents of m/e 228 and m/e 252 relative to m/e 234. Working conditions of the mass spectrometer were as follows: 70 electron volts, total emission 80 milliamperes, vacuum $5-6 \times 10^{-7}$ mm Hg, temperature of the ionization chamber 80 C, scan range m/e 226-254. Values of CHR and BP determined by mass spectrometry needed to be corrected by multiplying the value of CHR by 0.953 and the value of BP by 0.693 in the case of ambient air in Osaka because the values were affected by isomers of CHR and BP contained in the airborne particulate matter. Relative standard deviations of measured values of CHR and BP in the range of 0.1 to 50 nanog were 2%-7%, and analysis time of the mass spectrometry was 7 to 8 min/sample. The advantages of the technique are high sensitivity, excellent quantitative accuracy, and simple analytical procedure. (12 refs)

79-0298 Inverse Correlation Between Species Lifespan and Capacity of Cultured Fibroblasts to Convert

Benzo(a)pyrene to Water-soluble Metabolites. (Eng) Moore, C. J. (Dept. Microbiology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140); Schwartz, A. G. *Exp Cell Res* 116(2): 359-364; 1978.

Diploid lung and skin fibroblasts of eight mammalian species were cultured, and the ability of the fibroblasts to convert benzo(a)pyrene (BP) to water-soluble metabolites was determined. The rate of conversion was dependent on culture density, and it varied widely among different species. There was a very good inverse correlation between species life span and the metabolism of BP to water-soluble metabolites in the cultured fibroblasts of a given species. Peak BP metabolizing activity was in the order hamster > mouse = rat > guinea pig > rabbit > cow > elephant > human ($p < 0.01$), with a 240-fold difference in the activities of the most active species (hamster) and the least active (human). Since these cell systems have also shown a good inverse correlation between species life span and the biological activity of 7,12-dimethylbenz-(a)anthracene, the data suggest that the metabolism of polycyclic hydrocarbon carcinogens is closely related to life span in mammalian species. (22 refs)

79-0299 Retinoids as Well as Tumour Promoters Enhance Deacylation of Cellular Lipids and Prostaglandin Production in MDCK Cells. (Eng) Levine, L. (Dept. Biochemistry, Brandeis Univ., Waltham, MA, 02154); Ohuchi, K. *Nature* 276(5685): 274-275; 1978.

The effects of various retinoids on the deacylation of cellular lipids and production of prostaglandins (PG's) in dog kidney (MDCK) cells were studied. Incubation of MDCK cells with the trimethylmethoxyphenyl (TMMP) analog of retinoic acid (0.1 to 2.0 μ g/ml) resulted in increased production of PGE-2 and PGF-2 α . All other retinoids tested except retinyl palmitate also stimulated PG production to varying degrees. Deacylation of cellular lipids by 3 H-arachidonic acid-labeled cells was stimulated by cis-retinoic acid or TMMP-retinoic acid (2.0 μ g/ml). The level of stimulation was greater with the tumor-promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) than with the retinoids. The stimulating effects of TPA and TMMP-retinoic acid were synergistic, whereas those of TPA and cis-retinoic acid were not. The use of vitamin A and some of its analogs to prevent chemical carcinogenesis may, therefore, be premature; they may enhance, not inhibit, tumor formation. (21 refs)

79-0300 Neoplastic Potential in Stratified Epithelial Gradients Following Metaplasia Induced by Nutritional Deficiency of Vitamin A: An Interpretation. (Eng) Van Dyke, J. H. (Dept. Anatomy, Hahnemann Medical Coll., Philadelphia, PA). In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International

Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp; 707-725; 1977.

To investigate the fate of basal and suprabasal epithelial cells during tumorigenesis, metaplastic foci (cysts lined by stratified squamous epithelium) were induced in the thyroid and thymus glands of Wistar rats. In rats maintained on vitamin A-deficient diets to induce squamous cell metaplasias, thyroids were mitotically stimulated by the simultaneous dietary estrogen (2 mg/day allylthiourea) and carcinogen (2 mg/day 2-acetylaminofluorene) and thymuses by ip injection of estrogen (estradiol dipropionate 0.25 ml 2 x/wk). Induced metaplastic lesions were similarly stimulated during periods of reacquisition of vitamin A (when cell strata separate during typical epithelial repair), which resulted in neoplasms unique to particular cell-layer gradients. Basal cells from thyroid cysts eventually formed undifferentiated, carcinomatous masses. The cytotreticulum of the thymus produced abnormal thymic corpuscles that ultimately formed multiple cysts. Suprabasal cells from these metaplastic lesions produced "new growths" in both organs: thyroid cystadenomas and thymic spindle cell tumors. It is concluded that nests of suprabasal cells, deeply implanted in a propitious organ environment, are implicated in malignant transformation. When released from intact stratified squamous epithelium (cysts) during repair of metaplasia, these cells, improperly induced, may be a prime source of epithelial, glandular malignancies. (23 refs)

- 79-0301 Analysis of the Aryl Hydrocarbon Hydroxylase Assay.** (Eng) Yang, C. S. (Dept. Biochemistry, New Jersey Medical Sch., Coll. Medicine and Dentistry New Jersey, Newark, NJ, 07103); Strickhart, F. S.; Kicha, L. P. *Biochem Pharmacol* 27(19): 2321-2326; 1978.

The assay method and the properties of aryl hydrocarbon hydroxylase (AHH) were studied with Long-Evans rat liver microsomes. The assay was carried out by two methods: (1) the microsomes (initially at 15-20 C) were preincubated at 37 C, and then benzo[a]pyrene (BP) and NADPH were added to initiate the assay; and (2) BP was added to microsomes at 15-20 C, preincubated at 37 C, and then NADPH was added to initiate the reaction. The AHH activity obtained by method 1 was usually 60%-120% higher than that obtained by method 2. Several lines of study suggested that the microsomes can exist in two states. Binding of BP at temperatures lower than 20 C would limit the microsomes to a low activity state, whereas binding at temperatures above 25 C would enable the microsomes to exist in a high activity state. The molecular basis of these activity states remains to be investigated. The effects of acetone and methanol, both widely used solvents for BP, on AHH were also studied. AHH activities of control and phenobarbital-induced microsomes were higher with acetone as the solvent for BP, compared with methanol. The hydroxylase activity of 3-methylcholanthrene-induced microsomes, however, was slightly higher with methanol. (29 refs)

- 79-0302 Differences Between the Hydroperoxide-dependent and NADPH-Dependent Microsomal Aryl Hydrocarbon Hydroxylase Activities.** (Eng) Yang, C. S. (Coll. Medicine and Dentistry of New Jersey, Newark, NJ, 07103); Strickhart, F. S. *Biochem Pharmacol* 27(19): 2376-2378; 1978.

The hydroperoxide-dependent and NADPH-dependent microsomal aryl hydrocarbon hydroxylase (AHH) systems were compared with regard to the relative catalytic activities of cytochrome P-450- and cytochrome P-448-containing microsomes they contain, as well as the actions on them of specific inhibitors of the mono-oxygenase system. The results indicated that there is no parallelism between the NADPH- and hydroperoxide-dependent systems with regard to the AHH activities of the different types of microsomes. (16 refs)

- 79-0303 Effects of Dietary Cyclopropene Fatty Acids on the Mixed Function Oxidase System of the Rainbow Trout (*Salmo gairdneri*).** (Eng) Eisele, T. A. (Dept. Food Science and Technology, Oregon State Univ., Corvallis, OR, 97331); Nixon, J. E.; Pawlowski, N. E.; Sinnhuber, R. O. *J Environ Pathol Toxicol* 1(6): 773-778; 1978.

Dietary cyclopropene fatty acids (CPFA) in rainbow trout (*Salmo gairdneri*) decreased cytochrome P-450 and b₅ content and NADPH-cytochrome c reductase activity 67.8%, 22.0%, and 38.4%, respectively, compared with control-fed trout after 22 days. Dietary CPFA induced benzo(a)pyrene aryl hydrocarbon hydroxylase 37.5% over controls over the same time period. Microsomal protein levels were consistently lower in CPFA-fed trout throughout the experiment (74 days). The data suggest a possible mechanism by which dietary CPFA act as cocarcinogens. (25 refs)

- 79-0304 Epoxide Hydratase and Benzo(a)pyrene Monooxygenase Activities in Liver, Kidney and Lung after Treatment of Rats with Epoxides of Widely Varying Structures.** (Eng) Schmassmann, H. (Inst. Pharmacology, Univ., Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany); Sparrow, A.; Platt, K.; Oesch, F. *Biochem Pharmacol* 27(18): 2237-2245; 1978.

The effects of various epoxides on epoxide hydratase and benzo(a)pyrene monooxygenase activities were investigated in the rat liver, kidney, and lung in an effort to identify a selective inducer of epoxide hydratase. With respect to five measured monooxygenase parameters, trans-stilbene oxide (TSO) was found to selectively induce hepatic epoxide hydratase activity. (53 refs)

- 79-0305 Thin-Layer Chromatographic-Fluorometric Determination of Diethylstilbestrol in the Urine**

and Feces of Calves Being Fattened for Market. (Ger) Vogt, K. (Institut für Physiologie, Süddeutsche Versuchs- und Forschungsanstalt für Milchwirtschaft, 805 Freising-Weihenstephan, W. Germany). *Arch Lebensmittelhyg* 29(5): 178-181; 1978.

Diethylstilbestrol can be determined in bovine fecal and urine samples at a sensitivity of 10 nanograms/ml by thin-layer chromatography and fluorometry following treatment of the extract with 5-dimethylaminonaphthalenesulfonic acid. The use of diethylstilbestrol to fatten calves is illegal in West Germany. (15 refs)

79-0306 Metabolism of Diethylstilbestrol: Identification of a Catechol Derived from Dienestrol. (Eng) Weidenfeld, J. (Hadassah Medical Sch., Hebrew Univ., Jerusalem, Israel); Carter, P.; Reinhold, V. N.; Tanner, S. B.; Engel, L. L. *Biomed Mass Spectrom* 5(10): 587-590; 1978.

A catechol metabolite of diethylstilbestrol (DES) was formed after incubation of DES with mushroom tyrosinase or rat liver microsomes in the presence of oxygen and NADPH. Both catechols were further oxidized with periodate to form o-quinones and then condensed with o-phenylenediamine to form stable phenazines. The gas chromatographic retention times and mass spectrometric fragmentation patterns of these phenazines were identical to that of the phenazine prepared by oxidation of DES with potassium nitrosodisulfonate (Fremy's salt) and treatment of the resulting o-quinone with o-phenylenediamine. The high- and low-resolution mass spectra of the phenazine were consistent with its derivation from a catechol having two fewer hydrogens than DES. This is the first direct demonstration of the formation of a catechol metabolite of DES in vitro by both a mammalian and a plant enzyme system. (16 refs)

79-0307 Morphological and Functional Consequences of Prenatal Exposure to Diethylstilbestrol in the Rat. (Eng) Boylan, E. S. (Dept. Biology, Queens Coll. City Univ. New York, Flushing, NY, 11367). *Biol Reprod* 19(4): 854-863; 1978.

Pregnant Sprague-Dawley rats were treated with diethylstilbestrol (DES) during the second or third trimester (Tr) of gestation to determine the effects of exposure to DES in utero on the offspring. Total DES doses of 12,000, 1,200, 120, 60, 12, or 1.2 μ g were administered sc in two or three injections during Tr 2 or 3. A total dose of 120 μ g in Tr 3 allowed 62% of animals to deliver normally, whereas doses between 12,000 and 12 μ g in Tr 2 resulted in fetal retention or abortion in the majority of animals. The highest dose of DES resulted in prominent nipple development in both males and females in utero, and microscopic examination showed that the epithelial hood was lacking in nipples of female retained fetuses and neonates exposed to ≥ 120 μ g DES in either Tr 2 or 3.

Females exposed to 1.2 μ g or 120 μ g DES during Tr 3 had precocious opening of the vagina, and 8/15 of the animals exposed to 120 μ g DES were barren when mating was attempted. Of seven pregnant females that received 120 μ g DES, four gave birth to live pups, but the pups of only two mothers survived to weaning. Other abnormalities, such as incomplete fusion of the urethra, enlarged ovaries (including cysts or solid masses), and distended uterine horns and vaginas, were seen in 7/32 females exposed in utero to 120 μ g DES, but male offspring appeared unaffected by maternal DES treatment. This report confirms that DES is transported transplacentally in the rat and has effects on a variety of fetal tissues. (14 refs)

79-0308 Absorption and Glucuronylation of Diethylstilbestrol by the Rat Small Intestine. (Eng) Lasker, J. (Chemical Industry Inst. Toxicology, PO Box 12137, Research Triangle Park, NC, 27709); Rickert, D. E. *Xenobiotica* 8(11): 665-672; 1978.

The absorption and glucuronylation of (14 C)diethylstilbestrol (DES) were studied in situ in segments of male Sprague-Dawley rat small intestine with intact arterial supply and complete collection of venous blood. A 0.5 ml aliquot of 0.1, 1.0, 2.0, or 5.0 mM DES in isotonic saline-20% ethanol plus a tracer of 14 C-DES were instilled into the intestinal lumen, and venous blood collected for six 10-min periods. All methanol-soluble radioactivity in the intestinal venous blood, the luminal contents, and the intestinal tissue co-chromatographed with authentic DES or authentic diethylstilbestrol glucuronide. There was no difference between DES glucuronide formation in intestinal segments near the pyloric sphincter and in segments located near the ileocecal junction. The appearance of DES and DES glucuronide in the venous blood of aborally-located segments was dose-dependent from 0.1 to 5 mM, but in orally-located segments, an increase in DES concentration from 2 to 5 mM produced no increase in the content of DES or its glucuronide. DES and DES glucuronide content in the intestinal wall increased with increasing DES concentration in both regions of the intestine. In the lumen, however, DES-related materials increased with dose in oral segments, but there was no increase in the aboral segments when DES concentration was raised from 2 to 5 mM. Appearance of DES and DES glucuronide in the venous blood was independent of blood flow. The results suggest that intestinal glucuronylation during absorption may be significant over a wide range of concentrations in all regions of the intestine. (23 refs)

79-0309 Liver Tumours Associated with Oral Contraceptives. (Eng) Britton, W. J. (Royal Prince Alfred Hosp., Camperdown, NSW 2050, Sydney, Australia); Gallagher, N. D.; Little, J. M. *Med J Aust* 2(6): 223-227; 1978.

The case reports of five women (ages 21-30 yr) who were users of oral contraceptive agents (OCA) and who developed liver tumors are presented. All patients had been using OCA for periods ranging from 0.5 to 10 yr. One patient was originally investigated because of hepatomegaly, two noticed an abdominal mass themselves, one first complained of dull abdominal pain, and one suffered obstructive jaundice. The masses were successfully removed in three patients, and all were diagnosed as adenomas. The fourth patient, who also had an adenoma, suffered a massive intraabdominal hemorrhage during an attempted percutaneous liver biopsy, and eventually died from complications. The jaundiced patient had a well-differentiated primary hepatocellular carcinoma that invaded the biliary tree; she eventually died of liver failure. The adenomas were composed of uniform to slightly atypical hepatocytes arranged in cords or pseudoacini around secreted and retained bile. Bile ducts were only occasionally identified, and the usual lobular architecture was absent. Cell tumors were highly vascular, and differentiation of the vascular supply permits a planned surgical approach to the lesion. No one particular type of OCA was implicated as being causative. It is suggested that the diagnosis of liver tumor be considered in any OCA users presenting with obscure abdominal pain, hepatomegaly, an abdominal mass, or surgical emergency of hemoperitoneum. (30 refs)

- 79-0310 Liver Tumors and Oral Contraceptives: Pathology and Pathogenesis.** (Eng) Gindhart, T. D. (Dept. Pathology, Univ. California, San Francisco, CA, 94143). *Ann Clin Lab Sci* 8(6): 443-446; 1978.

Two case histories are reported to illustrate the different pathological features of hepatocellular adenoma (HCA), which is associated with oral contraceptive (OC) use, and focal nodular hyperplasia (FNH), which appears to be only coincidentally associated but with a particular hemorrhagic tendency. A 33-yr-old woman with a 7-yr history of OC use presented with right upper abdominal pain of 5 mo duration. During the 30 mo before presentation, she had taken an OC containing 2 mg chlormadinone acetate and 80 μ mestranol. Serum alkaline phosphatase was slightly elevated, but other serum indicators of liver condition were normal. Liver scan showed two HCA's, a 9-cm vascular mass and a 6-cm avascular mass. Microscopically, large hepatocytes arranged in haphazard plates accompanied by Kupffer cells were evident, but portal triads and bile duct proliferation were absent. The latter feature distinguishes FNH from HCA. Fibrosis was only present in a capsule surrounding the tumor. Case 2 was a 28-yr-old woman who had taken OC's intermittently for 9 yr until 10 mo prior to death from cervical carcinoma. A 1.5-cm-diameter, well-demarcated lesion of FCN was an incidental finding on autopsy. Microscopically, the lesion resembled regeneration nodules of cirrhosis. Enlarged hepatocytes arranged in plates and fibrous septa with bile duct proliferation were evident. Right upper quadrant pain with abdominal hemorrhage is the most common clinical presentation of HCA, a condi-

tion for which mestranol-containing preparations appear particularly hazardous. (22 refs)

- 79-0311 Combined Oral Contraceptives and Cancer of the Uterine Cervix.** (Nor) Nesheim, B. I. (No affiliation given). *Tidsskr Nor Laegeforen* 98(29): 1422-1423; 1978.

Two surveys covering 6,000 and 14,000 women, respectively, showed a positive correlation between the use of combined oral contraceptives and cervical cancer. The cancer risk increased with duration of use. (5 refs)

- 79-0312 Oral Contraceptives and Endometrial Cancer.** (Eng) Silverberg, S. G. (Colorado Regional Cancer Center, Univ. Colorado Sch. Medicine, Denver, CO, 80262). In: *Estrogens and Cancer. Proceedings of a meeting held by the Colorado Regional Cancer Center in Denver, Sept. 10, 1977.* Colorado Regional Cancer Center (Denver, CO): 197 pp; 73-87; 1978.

Of 30 endometrial tumors included in a registry of tumors developing in women < 40 yr taking oral contraceptives, 22 were Grade I adenocarcinomas, adenocanthomas, or secretory carcinomas. The only histologic difference between the registry tumors and those in 25 controls who had not received oral contraceptives was in the frequency of pure clear cell or secretory carcinomas or carcinomas with a focal secretory pattern (14/29 registry cases vs 2/25 controls). There was only one tumor-related death in the registry group, and myometrial invasion was observed in only 2/18 patients who underwent hysterectomy without prior radiation therapy. Two-thirds of the patients had taken sequential agents (eg, Oracon), and nine had taken combined agents (eg, estrogen and progestagen) that were prescribed in seven cases for vaginal bleeding or polycystic disease consistent with the Stein-Leventhal syndrome. The results indicate that different types of estrogens can have the same end effect on the endometrium. (32 refs)

- 79-0313 Estrogen Receptor in the Mammalian Liver: Effect of Metabolism on the Amount and Identity of Receptor-bound Estrogen.** (Eng) Weinberger, M. J. (Dept. Molecular Medicine, Mayo Clinic, Rochester, MN, 55901); Aten, R. F.; Eisenfeld, A. J. *Biochem Pharmacol* 27(20): 2469-2474; 1978.

Estrogen-liver interactions were studied by incubating liver slices from ovariectomized CD rats with 2,4,6,7-³H-estradiol [³H-E₂: specific activity 100 Ci/millimole (mmol), 200 disintegrations/min/femtomole (dpm/fmol)] or with 6,7-³H-E₂ (47 Ci/mmol, 100 dpm/fmol) in phosphate buffer. Macromolecule-bound radioactivity in purified cytosol and nu-

clear fractions was determined by gel filtration on Biogel P-10 columns. Max binding in both fractions occurred at a E_2 concentration of 5×10^{-8} M. Of the $^3H-E_2$ originally present in the medium, 97% was metabolized in < 15 min after incubation of the liver slices at 25 C. When testosterone (5×10^{-6} M) was added to medium containing submax $^3H-E_2$ concentrations, increased cytosol binding was observed after 5, 15, and 30 min, increased nuclear binding after 30 and 60 min. Hexobarbital (1×10^{-3} M) also increased nuclear radioactivity after a 1-hr incubation period. In the nuclear fraction, E_2 represented 52% and 2-hydroxyestradiol 36% of the radioactivity bound after the liver slices were incubated at 37 C for 1 hr. Diethylstilbestrol reduced the binding of these major metabolites (from approx 21,000 to 5,000 dpm/g liver), which suggested a specific interaction between the nuclear receptor and the two estrogens. Thus, the risk of liver tumors from oral contraceptives might be minimized by the use of estrogens that are metabolized preferentially to inactive derivatives in the liver. (16 refs)

- 79-0314 Treatment of Tall Girls with Estrogen.** (Eng) Crawford, J. D. (Children's Service, Massachusetts General Hosp., Boston, MA, 02114). *Pediatrics* 62(6, part 2, Suppl): 1189-1195; 1978.

The effects of using estrogens to curb the statural growth of tall girls are reviewed. One series of 100 girls was treated between 1955 and 1971 with 5 mg/day diethylstilbestrol (DES) and 5 mg/day norethindrone for the first 5 days of each mo. In another series of 26 girls, treated during 1968-1976, the DES was replaced by 0.25 mg/day ethinyl estradiol. Ovarian tumors were not encountered in these two series. One girl with a benign serous cystadenoma of the ovary that became symptomatic during treatment with 10 mg/day conjugated estrogens was found upon referral. Another girl was referred for increasing asymmetry of the breasts after 4 mo treatment with 5 mg/day DES. A large fibroadenoma mole was removed that probably existed before the start of treatment. In one patient of the second series, a nodule detected after 15 mo treatment with ethinyl estradiol proved to be a benign intraductal papilloma. (32 refs)

- 79-0315 Menopausal Therapy and Endometrial Pathology (Letter to Editor).** (Eng) Studd, J. (Dulwich Hosp., London SE22, England); Thom, M.; White, P. J. *Br Med J* 2(6148): 1369; 1978.

The dose schedule and treatment of 34 postmenopausal patients with endometrial hyperplasia who received hormone replacement therapy are discussed. Only 7 of the 29 patients with cystic glandular hyperplasia were receiving progestogen. Twelve of the 16 cases occurring with estrogen implants were associated with failure to take the prescribed norethisterone each month. The endometrial pathology was reversible in most cases with two courses of norethisterone. (no refs)

- 79-0316 Postmenopausal Estrogens and Endometrial Cancer: Clinicopathologic Correlations.** (Eng) Miller, A. (Dept. Pathology, Rush Medical Sch., Chicago, IL, 60612); Mullen, D.; Faraci, J. A.; Makowski, E. L.; Silverberg, S. G. In: *Estrogens and Cancer. Proceedings of a meeting held by the Colorado Regional Cancer Center in Denver, Sept. 10, 1977.* Colorado Regional Cancer Center (Denver, CO): 197 pp.; 35-42; 1978.

A preliminary study of the relationship between postmenopausal estrogen use and endometrial carcinoma in 114 patients is presented. The prevalence of diabetes, hypertension, and obesity in the 39 postmenopausal cancer patients who had received estrogen was significantly lower ($p < 0.001$) than in 75 postmenopausal cancer patients who had received no estrogen. There was less of a tendency to nulliparity or low parity among the estrogen users. The time between the last normal menstrual period and the diagnosis of carcinoma were similar among users and nonusers (13.6 and 12.0 yr, respectively), while the users had a shorter duration of symptoms before diagnosis (4.6 mo) than did the nonusers (7.8 mo). However, there was little evidence of differences in extent of disease between the two groups. Analysis of the histologic type and grade of the tumors seen in the two groups revealed one major difference: mixed adenosquamous carcinoma comprised 28% of cases in nonusers versus only 15% of cases in estrogen users. Vascular invasion was more common in hysterectomy specimens of the nonusers (10/54 cases) than in those of the users (2/37). Clear and ciliated cells occurred more frequently in estrogen-related tumors. The incidence of associated endometrial hyperplasia in either the curettage or hysterectomy specimen showed no significant difference between users and nonusers. Only 25% of users and 20% of nonusers failed to show hyperplasia in at least one slide. (23 refs)

- 79-0317 Differential Biological Activity of Estradiol Metabolites.** (Eng) Fishman, J. (Rockefeller Univ., 1230 York Ave., New York, NY, 10021); Martucci, C. *Pediatrics* 62(6, part 2, Suppl): 1128-1133; 1978.

The role of estradiol metabolism in the expression of the biological activity of the female sex hormone is reviewed. Estrone and estriol were found to be equivalent to estradiol as uterotrophic agents, but no uterotrophic activity was demonstrated with 2-hydroxyestrone. There is now considerable suggestive evidence that the spectrum of estrogenic action can be resolved by specific substances. (35 refs)

- 79-0318 Estrogen Use--Risk of Endometrial Carcinoma.** (Eng) Hoogerland, D. L. (Dept. Obstetrics-Gynecology, David Grant USAF Medical Center, Travis AFB, CA, 94535); Buchler, D. A.; Crowley, J. J.; Carr, W. F. *Gynecol Oncol* 6(5): 451-458; 1978.

A retrospective analysis was carried out to determine the rate of prior usage of exogenous estrogens in all endometrial adenocarcinoma patients treated in a Wisconsin hospital from 1960 to 1974. Rates for matched controls with a different gynecologic malignancy were also determined. Of the total 1,174 patients, 108/587 of the cases and 54/587 of the controls had estrogen exposure, yielding a relative risk of 2.2. The relative risk increased with duration of exposure from 1.2 for 1-6 mo usage to 6.7 for > 10 yr usage. Most of the endometrial lesions in exposed and unexposed patients were pure adenocarcinomas, and the bulk in both groups were low grade-early stage. Although there was a statistically significant increase in exposure rate from 1970 to 1974, the relative risk did not change significantly from earlier years. Hypertension, diabetes mellitus, and obesity were significant risk factors by themselves, but estrogen use did not appear to increase the risk in patients with these conditions. Estrogen users without these predisposing factors had a nonsignificantly higher relative risk (3.2) than those who did have them (2.0). An association between exogenous estrogens and endometrial carcinoma must be considered. (14 refs)

79-0319 Alternative Analytic Methods for Case-Control Studies of Estrogens and Endometrial Cancer. (Eng) Horwitz, R. I. (Robert Wood Johnson Clinical Scholar Program, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT, 05610); Feinstein, A. R. *N Engl J Med* 299(20): 1089-1094; 1978.

In a case-control study of estrogens and endometrial cancer, alternative sampling methods were used to eliminate the detection bias that arises from the increased diagnostic attention received by women with uterine bleeding after estrogen exposure. Two separate case-control studies were performed at the same institution. In Study 1, cases and controls were selected by the conventional procedure; Study 2, cases and controls were allowed to emerge from the results found in a group of women referred for the same intraendometrial diagnostic procedure. The patients source for Study 1 was 561 patients with gynecologic cancer, 119 of whom had endometrial cancer (first case group). In Study 2, there were 6,869 women who underwent dilatation and curettage or hysterectomy because of uterine bleeding, 149 of whom had endometrial cancer (second case group). Each endometrial cancer patient in both groups had an age- and race-matched control. The odds ratio in Group 1 was 11.98, that in Group 2 was 1.7. A

methodologic analysis demonstrated detection bias arising from the pattern of hospital referral and showed the way in which the bias is neglected or increased by conventional sampling procedures but reduced by the alternative procedure. The magnitude of the association between estrogens and endometrial cancer has been greatly overestimated because of detection bias; when an appropriate compensation for the bias is introduced, the odds ratio approaches a value much closer to 1. (14 refs)

See also:

- *(Rev.): 79-0001, 79-0002, 79-0003, 79-0004, 79-0005, 79-0006, 79-0007, 79-0008, 79-0009, 79-0010, 79-0011, 79-0012, 79-0013, 79-0014, 79-0015, 79-0016, 79-0017, 79-0018, 79-0019, 79-0020, 79-0021, 79-0022, 79-0023, 79-0024, 79-0025, 79-0026, 79-0027, 79-0028, 79-0029, 79-0030, 79-0031, 79-0032, 79-0033, 79-0034, 79-0035, 79-0036, 79-0037, 79-0038, 79-0039, 79-0040, 79-0041, 79-0042, 79-0043, 79-0044, 79-0045, 79-0046, 79-0047, 79-0048, 79-0049, 79-0050, 79-0051, 79-0052, 79-0053, 79-0054, 79-0055, 79-0057, 79-0058, 79-0059, 79-0061, 79-0063, 79-0068, 79-0075, 79-0087.
- *(Phys.): 79-0321, 79-0325, 79-0334, 79-0338, 79-0362, 79-0374, 79-0377, 79-0378, 79-0379, 79-0380, 79-0382, 79-0383, 79-0385, 79-0386, 79-0389, 79-0390, 79-0396.
- *(Viral): 79-0405, 79-0414, 79-0432, 79-0453, 79-0474.
- *(Immun.): 79-0484, 79-0485, 79-0493.
- *(Path.): 79-0501, 79-0517, 79-0522.
- *(Epid-Biom.): 79-0532, 79-0534, 79-0536, 79-0537, 79-0538, 79-0540, 79-0541, 79-0542, 79-0551, 79-0552, 79-0553, 79-0555, 79-0570, 79-0571, 79-0572, 79-0573, 79-0574, 79-0575, 79-0576, 79-0577, 79-0578, 79-0579, 79-0580, 79-0581.

PHYSICAL CARCINOGENESIS

- 79-0320 Estimation of Inhalation Doses from Airborne Releases Using Gross Monitors.** (Eng) Goldstein, N. P. (Westinghouse R & D Center, Pittsburgh, PA, 15235). *Health Phys* 35(5): 675-683; 1978.

The problem of determining inhalation doses from various effluent streams of nuclear power plants by using the results from gross monitoring of airborne releases is considered. This type of monitor will accurately indicate dose, regardless of the isotopic makeup of a release, if its response to each isotope is proportional to the dose factor of that isotope. Gross beta and gross gamma counters were compared with respect to this criterion. Beta counters provide a better estimate of the dose than did gamma counters, as determined by using published power-plant emission data. A variety of other mathematical response functions were also considered but their dose-estimating capabilities were not better than the straight beta response. Although there is a basic limitation in the dose estimation capabilities of gross counters, it is concluded that reasonably accurate estimates of av dose can be achieved using properly selected gross counters and that significant errors can result with improper ones. (8 refs)

- 79-0321 A Perspective on the Radiation Protection Problem and Risk Analysis for the Nuclear Era.** (Eng) Vohra, K. G. (Dept. Atomic Energy, Bhabha Atomic Res. Centre, Bombay, India). *Int Atomic Energy Agency Bull* 20(5): 35-43; 1978.

A comparative analysis of the health risks resulting from exposure to ionizing radiation and to toxic chemical substances released from fossil fuel-burning facilities is presented to assess the relative risks of generating power by nuclear and fuel-burning methods. Quantitative risk from ionizing radiation can be extrapolated from existing data, assuming low dosage linearity and absence of a threshold. This analysis generates a risk value of 200 cancer deaths/million population/rem/yr for individuals continually exposed to 1 rem/yr over a lifetime. Natural radiation from all sources is calculated to be 100 millirem (mrem)/yr, which (based on the given risk calculation) leads to 1000 to 2000 deaths/million/yr due to spontaneous radiation. For comparison, the exposure from a nuclear power station is approx 5 mrem/yr, resulting in one excess cancer death/million/yr; the exposure from diagnostic radiation is 20-100 mrem/yr, generating an additional 10 deaths/million/yr. Lung cancer incidence has risen steadily for 20 yr, and a regression analysis shows that an increment of approx 152 lung cancer deaths/million/yr/ton of coal consumed/person has been contributed in England and Wales by air pollution. The specific coal combustion pollutant benzo(a)pyrene (BP), at a dose equivalent of 1 ng/meter³ (m³)

(actual concentrations in world cities are 1-4 ng/m³) results in excess lung cancer deaths (48/million/yr). Although BP is only one carcinogen present in combusted fuels and lung cancer is only one possible resulting disease, this last risk value serves as a quantitative proof of the relative hazards of the two power generating processes. It is concluded that nuclear power plants are safer than combustion-driven plants for generating energy. (14 refs)

- 79-0322 Transformation of Mouse C3H/10T1/2 Cells by Single and Fractionated Doses of X-Rays and Fission-Spectrum Neutrons.** (Eng) Han, A. (Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL, 60439); Elkind, M. M. *Cancer Res* 39(1): 123-130; 1979.

A mouse embryo-derived cell line, C3H/10T1/2, was used to measure the frequency of in vitro neoplastic transformation induced by 50-kilovolt peak x-rays and by fission-spectrum neutrons from the JANUS reactor at the Argonne National Laboratory. The transformation frequency after single x-ray doses rose exponentially, reaching a plateau at about 3×10^{-3} transformant/survivor. The induction curve following single neutron doses, although qualitatively similar, initially rose more steeply and then leveled off at a max of about 6×10^{-3} transformant/survivor. For both radiations, the transformation frequency varied with changes in the number of viable cells per dish, showing about a 10-fold decrease in transformation frequency when the number of viable cells per 90-mm dish was increased from about 300 to about 1,000. Fractionation of the total x-ray dose of 700 rads resulted in an approx six-fold increase in survival and a reduction in transformation frequency over a 16-hr interval. Fractionation of the total neutron dose of 378 rads had no effect on cell survival, and transformation frequency declined by a factor of only about 1.7 at most over a 24-hr period. Cells derived from transformed foci formed fibrosarcomas when injected into appropriately treated mice. (44 refs)

- 79-0323 Some Major Statistical Comments on "Radiation Exposures of Hanford Workers Dying from Cancer and Other Causes" (Letter to Editor).** (Eng) Gertz, S. M. (Porter-Gertz Consultants, Inc., Radiological Protection and Environmental Services, 76 Rittenhouse Place, Ardmore, PA, 19003). *Health Phys* 35(5): 723-724; 1978.

A previous conclusion that low-level radiation exposure caused cancer in Hanford workers was not supported by the data or analyses presented. Because an improper control group (cancer deaths of white US men in 1960) was used, the

study failed to prove an increase in cancer deaths in the examined population. It also failed to show that those dying from cancer received a greater absorbed dose than those who died from other causes, it failed to show an increase of cancer deaths with increased absorbed doses, and it used an inappropriate statistical procedure to determine those cancers with radiation associations. (1 ref)

79-0324 Role of Neutrons in Late Effects of Radiation Among A-Bomb Survivors (Meeting Abstract).

(Eng) Beebe, G. W. (Clinical Epidemiology Branch, NCI, Bethesda, MD, 20014); Land, C. E.; Jablon, S. *Health Phys* 35(6): 883; 1978. (1 ref)

79-0325 Mammary Carcinogenesis in Rats After X- and Neutron-Irradiation and Oestrogen Administration (Meeting Abstract).

(Eng) Broerse, J. J. (Radiobiological Inst. TNO, Rijswijk, Netherlands); Knaan, S.; van Bekkum, D. W.; Hollander, C. F.; Nooteboom, A. L.; Van Zwieten, M. J. *Int J Radiat Biol* 34(6): 572-573; 1978. (no refs)

79-0326 Studies of Tumour Induction in Long-Term Surviving Rhesus Monkeys Following Whole-Body X- and Neutron-Irradiation (Meeting Abstract).

(Eng) van Zwieten, M. J. (Inst. Experimental Gerontology TNO, Rijswijk, Netherlands); Zurcher, C.; Hollander, C. F.; Borerse, J. J. *Int J Radiat Biol* 34(6): 572; 1978. (no refs)

79-0327 Leukemic Risk from Neutrons and Gamma Rays (Meeting Abstract).

(Eng) Kerr, G. D. (Health and Safety Res. Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830). *Health Phys* 35(6): 884; 1978. (no refs)

79-0328 Influence of Radiation Exposure Rate on Somatic Mutation Frequency and Loss of Reproductive Integrity in *Tradescantia* Stamen Hairs.

(Eng) Ichikawa, S. (Biology Dept., Brookhaven Natl. Lab., Upton, NY, 11973); Nauman, C. H.; Sparrow, A. H.; Takahashi, C. S. *Mutat Res* 52(2): 171-180; 1978.

The influence of gamma irradiation on somatic mutation frequency and the loss of reproductive integrity in *Tradescantia* stamen hair cells was examined. *Tradescantia* clone 02 was irradiated with gamma-rays at 29.3 R/min for 1.5-12 min (high exposure rate (HER)) or 0.026-0.52 R/min for 16 hr (low exposure rate (LER)). *T. blossfeldiana* was similarly irradiated with 256 R/min for 1.5-12 min or 0.52-41.7 R/min for 16 hr. Somatic mutations were scored as pink cells in otherwise blue terminal hairs, and loss of reproductive integ-

rity was scored as stunting of the stamen hairs. Somatic mutations were first noted in clone 02 on day 6 after HER and day 7 after LER; the frequency of mutational events peaked on days 8-12. At LER, the slope of the mutation-response curve was 0.98, giving a mutation frequency of 9.2×10^{-4} pink mutations/hair/R. The HER mutation-response slope was 1.24, increasing from 1.2×10^{-3} pink mutations/hair R at lowest exposure (38R) to 1.6×10^{-3} pink mutations/hair at highest exposure (114R). Maximum frequencies of stunted hairs were observed at 10-15 days in clone 02 and at 13-25 days in *T. blossfeldiana*. Maximum production was generally observed later at higher exposures and exposure rates. The D_0 values (doses at which 37% of the treated cells survived) for clone 02 were 154 R and 270 R for HER and LER, respectively, and the analogous figures for *T. blossfeldiana* were 720 R and 1880 R. These D_0 's are within the range normally determined for mammalian cells, indicating that these systems may be comparable in this regard. (44 refs)

79-0329 Mutation in *Escherichia coli* During Photodynamic Inactivation and Subsequent Holding in Buffer.

(Eng) Basu, S. (Dept. Physics, Calcutta Univ. Coll. Science, 92 Acharya Prafulla Chandra Road, Calcutta 700 009, India); Bagchi, B. *FEBS Lett* 96(1): 26-30; 1978.

The level of mutation induced in *Escherichia coli* B/r cells during dye-sensitized irradiation and subsequent holding of the cells in buffer at 37 C in the dark was determined. The cells were sensitized with acriflavine (15 μ g/ml) in the dark for 45 min and then irradiated with visible light flashes of 9.5×10^3 joules/m² or with low doses of 253.7-nanometer UV light. Mutagenicity was scored by counting the number of histidine revertants after the cells were plated on partially enriched minimal agar. A high level of mutation occurred both during dye-sensitized irradiation and subsequent holding in buffer, indicating that most of the damage in the photodynamically treated cells was incapable of being repaired by an error-free excision repair pathway. The slope of the log of the mutation frequency vs log of the radiation dose (both visible and UV) had a slope near unity, indicating a linear dependence. Reversion frequency also increased as a function of holding time. The effect of visible light alone on low-UV mutagenesis was almost negligible compared with that of dye + visible light. The high level of mutation induced by low-dose UV may be due to a loss of immunity of the newly synthesized DNA to error-prone repair. (30 refs)

79-0330 X- or γ -Ray Leukemogenesis in Humans.

(Eng) Rosen, P. (Dept. Physics and Astronomy, Univ. Massachusetts, Amherst, MA, 01003). *J Theor Biol* 75(4): 603-606; 1978.

A proposed model for ionizing radiation-induced leukemogenesis in humans is an extension of an earlier model for UV-induced carcinogenesis, in which a mutation occurs in

the operator region of a gene controlling the synthesis of divisional proteins (proteins that are signals for mitosis initiation). For γ -rays, thymine base damage is assumed to be the major damage causing neoplastic transformation. The model was used to calculate the frequencies of myeloid leukemia (ML). It was assumed that there exists a radiation target on the genome that, when struck, initiates events leading to ML and that there exists a repressible gene for WBC maturation. Thus, the following scenario can be assumed: two repressors account for a sequential repression of gene expression. Inactivation of the first repressor (by x-ray damage to its corresponding operator region) permits synthesis of the second, which will repress the expression of the WBC maturation gene. Assumption is also made of a dose-squared relationship based on a two-hit process in which one hit damages a gene specifying a repair process and the second causes a leukemogenic mutation. A mutation frequency per locus per rad of approx 2×10^{-7} was used in an equation that estimates the probability of leukemogenesis per cell. This probability was calculated for four different doses, and the data were compared with previous data. At 200 rads, the probability is 10^{-4} /cell. (22 refs)

79-0331 Evidence on the Nature of Radiation-induced Mutations in Cultured Mammalian Cells (Meeting Abstract). (Eng) Cox, R. (MRC Radiobiology Unit, Harwell, Didcot, Oxfordshire, England); Masson, W. K. *Int J Radiat Biol* 34(6): 554; 1978. (no refs)

79-0332 Low Level Continuous and Acute Radiation Effects on Lymphocyte Transformation and Repair Capability (Meeting Abstract). (Eng) Kol, R. (Radiobiology Dept., Israel Atomic Energy Commission, Nuclear Res. Centre-Negev, Beer Sheba, Israel); Riklis, E. In: *Program and Abstracts of the 12th International Leukocyte Culture Conference held in Beer Sheba, 25-30 June, 1978*. Ben Gurion University of the Negev. (Beer Sheba, Israel): 347 pp.; p. 39; 1978. (no refs)

79-0333 Tests of the Linearity Assumption in the Dose-Effect Relationship for Radiation-induced Cancer (Meeting Abstract). (Eng) Cohen, A. F. (Univ. Pittsburgh, Pittsburgh, 15213, PA); Cohen, B. L. *Health Phys* 35(6): 915-916; 1978. (no refs)

79-0334 Dose-Response Relationships Implied by Stochastic Model of Carcinogenesis (Meeting Abstract). (Eng) Brodsky, A. (Office Standards Development, United States Nuclear Regulatory Commission, Washington, DC, 20555). *Health Phys* 35(6): 916; 1978. (1 ref)

79-0335 R.b.e.-LET Relations for Induction of Reproductive Death and Chromosome Aberrations in Mammalian Cells (Meeting Abstract). (Eng) Barendsen, G. W. (Radiobiological Inst. TNO, Rijswijk, Netherlands). *Int J Radiat Biol* 34(6): 555; 1978. (no refs)

79-0336 Neutron r.b.e. for Chromosomal Aberrations and Sister Chromatid Exchanges (Meeting Abstract). (Eng) Clare, G. (Leeds Univ. Dept. Radiotherapy, Regional Radiotherapy Centre, Cookridge Hosp., W. Yorkshire, England). *Int J Radiat Biol* 34(6): 554-555; 1978. (no refs)

79-0337 Myeloid Leukemia in X-Irradiated CBA/H Mice (Meeting Abstract). (Eng) Major, I. R. (MRC Radiobiology Unit, Harwell, Didcot, Oxfordshire, England); Mole, R. H. *Int J Radiat Biol* 34(6): 571; 1978. (no refs)

79-0338 Role of Testosterone in the Development of Radiation-induced Prostate Carcinoma in Rats. (Eng) Takizawa, S. (Dept. Cancer Res., Res. Inst. Nuclear Medicine and Biology, Hiroshima 734, Japan); Hirose, F. *Gann* 69(5): 723-725; 1978.

The effect of testosterone (TS) on the development of x-ray-induced prostate cancer was studied in male Sprague-Dawley rats. Five-week-old rats were castrated and treated with TS (monthly im injections of 2.5 mg for 2 mo, then 5.0 mg) for their life span. At 6 wk of age, they were irradiated in the pelvic region with a total of 5,000 rads of x-rays delivered in five doses at intervals of 2 or 3 days. Other groups of rats were castrated and irradiated locally, irradiated locally, or untreated. Prostate cancer developed only in the hormone-replaced rats, and the incidence was 4/12 at 7-11 mo after irradiation. There was 1 moderately differentiated adenocarcinoma, 1 undifferentiated carcinoma, and 2 mucus-secreting adenocarcinomas. Metaplastic and atypical growth of the glandular epithelium was found in the ventral and dorsal lobes in both irradiated, intact (3 cases) and hormone-replaced rats (6 cases). These lesions might be a distorted regeneration of glandular epithelia, and they may lead to a neoplasm. The absence of prostate tumors in the irradiated, intact rats was unexpected. Apparently, Sprague-Dawley rats are resistant to the tumorigenic action of x-rays in the prostate gland (compared with Wistar rats). It is concluded that TS acted as a promoter for the development of prostate cancer and precancerous lesions. It is not known whether TS per se is a carcinogen. (7 refs)

79-0339 The Ratio of Cytochromes in Radiation-induced Leukemia Cells of Mice. (Eng) Irie, S. (Radi-

tion Center Osaka Prefecture, Osaka, Japan); Okumoto, M.; Takamori, Y. *Radiat Res* 76(2): 339-348; 1978.

Cytochrome aa₃, b, c₁, and c levels were compared in normal thymocytes from NIH Swiss mice (NT), a spontaneous thymic lymphoma of AKR mice (STL), a radiation-induced thymic lymphoma (RTL) in NIH Swiss mice, and three different lines of transplantable ascites thymic lymphoma cells (TL-69, TL-75, and TL-76). Cytochrome content was determined from difference spectra between the anaerobic and aerobic states at room temperature and at the temperature of liquid nitrogen. The concentration of cytochrome aa₃ was 77 picomoles (pmol)/mg protein in NT, 80 in STL, and 97 in RTL, but it decreased to 70, 58, and 61 pmol/ng protein in TL-76, TL-75, and TL-69 cells, respectively. The cytochrome c + c₁ concentration was similar in STL, TL-75, and NT (94-106 pmol/ng protein), but it increased to 129 pmol/ng in RTL and 145 pmol/ng in TL-69 cells. The cytochrome b level increased to 107 and 105 pmol/ng in STL and RTL, but the TL cell levels were similar to that of NT (74 pmol/ng). The c₁/aa₃ ratios in all tumor cells and the c + c₁/aa₃ ratios in the two primary lymphomas were comparable to those in NT, but the c + c₁/aa₃ ratio in the TL cells rose gradually with successive passage in vivo. Wt gain and survival studies in RF and NIH mice inoculated ip with 1 x 10⁷ TL-69 or TL-75 cells indicated that TL-69 cells grew more rapidly in the peritoneal cavity of mice and was the more virulent tumor cell line. (27 refs)

79-0340 The Induction of Dicentric Chromosome Aberrations in Human Lymphocytes By Unequal Split Doses of X-Radiation. (Eng) Purrott, R. J. (Natl. Radiological Protection Board, Harwell, Didcot, Oxfordshire, England); Reeder, E. J. *Mutat Res* 52(2): 291-293; 1978.

Dicentric aberration yields induced in human lymphocytes by 250-kilovolt peak x-rays given in single exposures or in two unequal dose fractions were studied. Whole-blood samples from a healthy donor were irradiated with two pairs of unequal doses (100 + 300 or 300 + 100, and 100 + 500 or 500 + 100 rads), with each fraction being delivered 24 hr apart, or with unsplit control doses of 100, 200, 300, 400, 500, and 600 rads. The minicultures were incubated with colcemid, and complete metaphases were analyzed for dicentric chromosomes. The number of dicentrics per cell (d/c) was 0.89 for 100 + 300 rads, 0.81 for 300 + 100 rads, 1.88 for 100 + 500 rads, and 1.90 for 500 + 100 rads. There was no significant difference between the two dicentric yields for each total dose, indicating that the size of the initial fraction does not influence overall aberration yield. In addition, the dicentric yields for all fractionated exposures were lower than their unsplit value of 1.02 (400 rads) and 2.11 (600 rads) d/c. For the 100/300 pairs, the observed yields agreed closely with the predicted additive value of 0.84 d/c; the 100/500-rad yields were closer to the additive value (1.78 d/c) than the unsplit value. Therefore, the difference between observed and expected baselines in dicentric yield found in

a previous dose-fractionation study cannot be explained on the basis of radiation affecting break-initiation or repair processes. (4 refs)

79-0341 A Somatic Dose Index for Diagnostic Radiology. (Eng) Laws, P. W. (Dickinson Coll., Carlisle, PA, 17013); Rosenstein, M. *Health Phys* 35(5): 629-642; 1978.

A somatic dose index is illustrated for an adult patient undergoing typical diagnostic radiology. The index was formulated by applying the relative sensitivity of the human body to each of the most important somatic effects and using the absorbed dose in the affected organs. This quantity was then used to convey a cumulative somatic impact and was computed for common radiographic views in diagnostic radiology as a function of beam quality for a nominal 1R entrance exposure. Since risk coefficients for cancer induction by radiation are different for men and women (two studies of radiation-induced carcinogenesis are reviewed including a table of risk coefficients and relative severities for selected organs), the somatic dose indices for radiographic examinations are displayed separately for men and women using different linear scales. Mammographic, thoracic spine (female), and rib (female) examinations have the highest somatic detriment to the individual, under the selected typical conditions. The next level of somatic detriment for both men and women is caused by upper gastrointestinal (GI), barium enema, and lumbosacral spine examinations. When the entire population somatic dose index was calculated, the population somatic detriment associated with mammography is 2 times greater than that for any other examination, followed by male and female upper GI examinations. Two other radiation risks (in utero exposure and genetically significant dose) are briefly reviewed. (18 refs)

79-0342 Chromosome Distribution Study in Peripheral Blood Lymphocytes from X-Ray Exposed Subjects (Meeting Abstract). (Eng) Verschaeve, L. (Laboratorium voor Antropogenetica, Vrije Universiteit Brussels, Brussels, Belgium); Kirsch-Volders, M.; Poma, K.; Hens, L.; Susanne, C. In: *Program and Abstracts of the 12th International Leukocyte Culture Conference held in Beer Sheva, 25-30 June, 1978*. Ben Gurion University of the Negev. (Beer Sheva, Israel): 347 pp.; p. 80; 1978. (no refs)

79-0343 A Second Brain Tumour and Irradiation. (Eng) Robinson, R. G. (Dept. Surgery, Univ. Otago Medical Sch., Dunedin, New Zealand). *J Neurol Neurosurg Psychiatry* 41(11): 1005-1012; 1978.

The cases of three patients who had a primary brain tumor that was managed by radiotherapy and who developed a sec-

and brain tumor of a different type 21 yr or more later are reported. Case 1 was a man born in 1935 who received approx 4,000 rads over 23 days for a mass in the third ventricle in 1945. An 18-g circumscribed pineal teratoma was subsequently removed. In 1971, a right frontal tumor was discovered after complaints of left hemiparesis. Upon necropsy, an extensive astrocytoma Grade 4 (glioblastoma multiforme) was noted. Case 2, a man born in 1915, was treated in 1951 with 2,750 rads over 39 days following removal of a 25-g transitional meningioma from the sphenoidal ridge. After readmission in 1972, a large neoplastic cyst containing 50 ml of xanthochromic fluid was discovered, and it was diagnosed as astrocytoma Grade 3. Case 3, who was born in 1941, received 3,000-3,500 rads to the total nervous system over 3 wk for a cerebellar round-cell tumor in 1953. She was admitted again in 1975 because of visual defects and was diagnosed with a suprasellar meningioma (30-mm in diameter) that had encircled the right optic nerve. Evidence in the literature shows that moderate to high doses of ionizing radiation given in childhood are associated with a late risk of developing a meningioma. There is insufficient evidence to implicate ionizing radiation in the etiology of gliomas. (35 refs)

- 79-0344 Neck Radiation and Hyperparathyroidism (Letter to Editor).** (Eng) Taylor, D. A. (Kaiser Foundation Hosp., Fontana, CA, 92335); Palmer, F. J.; Sawyers, T. M. *Ann Intern Med* 89(6): 1012-1013; 1978.

Of 66 patients with hyperparathyroidism seen over a 4-yr period, 6 (5 women, 1 man) had received previous neck irradiation. Four of these six patients underwent neck exploration: three had solitary parathyroid adenomas and one (the man) had hyperplasia of all four glands. (4 refs)

- 79-0345 Hemangiosarcoma Subsequent to Radiotherapy for a Hemangioma in Infancy.** (Eng) Bennett, R. G. (Emory Univ. Clinic, 1365 Clifton Road, Atlanta, GA, 30322); Keller, J. W.; Ditty, J. F. *J Dermatol Surg Oncol* 4(11): 881-883; 1978.

A 31-yr-old white man developed a hemangiosarcoma at the site of a hemangioma that had been treated 30 yr previously by x-rays. Only two similar cases could be found in the literature. (19 refs)

- 79-0346 A Review of One Hundred and Fifty Thyroidectomies Following Prior Irradiation to the Head, Neck, and Upper Part of the Chest.** (Eng) Wagner, D. H. (Chicago, IL); Recant, W. M.; Evans, R. H. *Surg Gynecol Obstet* 147(6): 903-908; 1978.

The records of 150 patients who had received prior irradiation to the head, neck, and upper part of the chest and who

subsequently underwent thyroid surgery due to identification of nodules upon technetium thyroid scan or palpation were analyzed. Most patients were 20-40 yr old, and approx 66% had been irradiated between the ages of 2 and 6. There were 48 thyroid carcinomas in this series, of which only 17 were recognized preoperatively or at operation. Eighteen other gross lesions were diagnosed on permanent sections, and 13 occult carcinomas diagnosed only after microscopic examination of thyroid tissue. The male:female ratio in both the benign and malignant tumor groups was 1:1, and the latent period from radiation exposure to time of operation for both groups was approx 20-30 yr. Of the 30 carcinoma patients who had a total thyroidectomy, 16 originally underwent a lesser procedure and required reoperation when carcinoma was confirmed on permanent sections. Of these 16 patients, 11 had residual carcinoma: 3 in the same lobe, 6 in the opposite lobe, and 2 in both lobes. This finding confirms the multifocal nature of the disease. The technetium scan was reliable for identifying thyroid nodules; physical examination was less accurate. (11 refs)

- 79-0347 Laryngeal Malignancy Following Iodine-125 Therapy for Thyrotoxicosis.** (Eng) McKillop, J. H. (Univ. Dept. Medicine, Royal Infirmary, Glasgow G4 0SF, Scotland); Doig, J. A.; Kennedy, J. S.; Thomson, J. A.; Greig, W. R. *Lancet* 2(8101): 1177-1179; 1978.

The development of an unusual laryngeal malignancy (spindle cell sarcoma) in a patient who received iodine-125 therapy is reported. A 52-yr-old woman presented with a laryngeal sarcoma 8 yr after receiving two 30-mCi doses of ^{125}I for thyrotoxicosis. The facts that extrathyroidal tissue receives a higher radiation dose of low-energy photon radiation from ^{125}I than from an equivalent microcurie dose of iodine-131 and that the tumor was of a type that rarely arises spontaneously in the larynx suggest a possible link between the development of the tumor and ^{125}I therapy. (16 refs)

- 79-0348 Late Radiation Effects in the Thyroid Gland: A Severe Sequela of Reactor Accidents.** (Swe) Walinder, G. (Natl. Defense Res. Inst., S-172 04 Sundbyberg, Sweden). *Lakartidningen* 75(25): 2479-2480; 1978.

An increased incidence of benign tumors and cancer of the thyroid gland was observed in the population of the Marshall Islands 22 yr after exposure to radioiodine following an atomic bomb test. The calculated thyroid dose was 139-137 rads. (no refs)

- 79-0349 Thyroid Gland Formation from Inocula of Monodispersed Cells: Early Results on Quantitation, Function, Neoplasia and Radiation Effects.** (Eng) Clifton, K. H. (Radiobiology Laboratories, Dept. Human

Oncology, Wisconsin Clinical Cancer Center, Univ. Wisconsin Medical Sch., Madison, WI, 53706); DeMott, R. K.; Mulcahy, R. T.; Gould, M. N. *Int J Radiat Oncol Biol Phys* 4(11/12): 987-990; 1978.

The results of a quantitated injection of monodispersed thyroid cells into the inguinal fat pads and the interscapular white fat pad of histocompatible thyroidectomized Fischer rats were studied. One group of animals was given a low-iodine diet and deionized water after grafting, and some of these animals were also given ^{125}I -iodine ip 6 hr before killing. Radioiodine uptake at the graft site was correlated with the number of cells inoculated and with increase in body wt after grafting. Irradiation of the cell suspension prior to grafting increased the number of cells necessary to achieve a particular degree of radioiodine uptake. Functional thyroid follicles developed at the graft sites, the number being related to the number of thyroid cells injected. These thyroid structures were able to concentrate iodine and support body growth. Two carcinomas and five adenomas developed in seven rats that received irradiated cells and adenomas developed in two rats that received nonirradiated cells. One of the carcinomas was highly undifferentiated and had metastasized to the lungs. (12 refs)

79-0350 Aerodynamic and Dissolution Behavior of Fume Aerosols Produced During the Combustion of Laser-ignited Plutonium Droplets in Air. (Eng) Raabe, O. G. (Dept. Radiological Sciences, Sch. Veterinary Medicine, Univ. California, Davis, CA, 95616); Teague, S. V.; Richardson, N. L.; Nelson, L. S. *Health Phys* 35(5): 663-674; 1978.

The aerodynamic and dissolution properties of fume aerosols produced by high temperature burning in air of single 50-500 μm -diameter droplets of gallium-stabilized, delta-phase plutonium (Pu) metal ignited with a laser were studied. Mass balance and aerosol measurements demonstrated that essentially all the Pu lost from the burning droplet (up to 40%) became aerosolized. Electron microscopy showed that these aerosols consisted primarily of web-like chains of ultrafine crystalline (cubical) particles (4-100 nanometers on side) and a few nearly spherical, discrete particles as large as 0.5 μm . Aerodynamic size distribution determined by using both the cascade impactor and spiral duct centrifuge samplers indicated that these aerosols were in the respirable range with activity median aerodynamic (resistance) diameters of 1-2 μm . In vitro dissolution studies demonstrated higher dissolution rates than normally exhibited by plutonium oxide; the expected dissolution half-time for the fume aerosols was predicted to be 100-700 days depending upon unit particle sizes. These shorter-than-expected half-times suggest that small particulate components become mobilized in the dissolution solvent. Such small particles could pass into the blood capillaries from the lung if inhaled and would be expected to have chemically reactive surfaces, as if chemical dissolution had occurred. (39 refs)

79-0351 Short-Term Metabolism of Inhaled Monodisperse $^{239}\text{PuO}_2$ in the Dog: Effect of Particle Size (Meeting Abstract). (Eng) Guilmette, R. A. (Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P.O. Box 5890, Albuquerque, NM, 87115); Diel, J. H.; Mewhinney, J. A.; Mo, T. *Health Phys* 35(6): 888; 1978. (no refs)

79-0352 Inhalation Toxicology of Industrial Plutonium and Uranium Oxide Aerosols. II. Deposition, Retention and Dosimetry (Meeting Abstract). (Eng) Stanley, J. A. (Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P.O. Box 5890, Albuquerque, NM, 87115); Eidson, A. F.; Mewhinney, J. A.; Mo, T. *Health Phys* 35(6): 888; 1978. (no refs)

79-0353 Plutonium Aerosol Characterization Inside Safety Enclosures at a Demonstration Mixed-Oxide Fuel Fabrication Facility. (Eng) Raabe, O. G. (Radiobiology Lab., Univ. California, Davis, CA); Newton, G. J.; Wilkinson, C. J.; Teague, S. V.; Smith, R. C. *Health Phys* 35(5): 649-661; 1978.

The atmospheres inside glove boxes in which plutonium oxide and uranium oxide were being used to fabricate reactor fuel pellets were sampled. A seven-stage cascade impactor was used to determine the aerodynamic size distribution and concentration, a spiral-duct aerosol centrifuge was used to study the characteristics of the particles with respect to aerodynamic equivalent size, and a point-to-plane electrostatic precipitator was used to take samples for electron microscopy. The median gross alpha activity concentrations in the glove box determined with the impactor samples was 45 nCi/liter. Alpha spectroscopy showed that the alpha activity was uniformly associated with two distinct energy peaks, one representing the ^{239}Pu - ^{240}Pu (5.1 megaelectronvolts (MeV)) and one representing ^{238}Pu and ^{241}Am (5.5 MeV). In the powder-mixing operation, the aerosol size distributions had activity median aerodynamic diameters (AMAD) of 1.9 μm and geometric standard deviations of 1.59. For the centerless grinding operation, the size distribution had an AMAD value of 2.3 μm and geometric standard deviation of 1.6. Some of the aerosols had sufficient electrostatic charge to alter sample collection if a discharger was not used. In vitro measurement of dissolution in a lung simulant predicted a half-time for inhaled material from the blending-mixing operation of 28-200 days and from the centerless grinding operation of 3-6 yr. Thus, both types of particles demonstrated higher solubility than reported for laboratory aerosols of high temperature-treated $^{239}\text{PuO}_2$. (10 refs)

79-0354 Urinary Plutonium Excretion Following Plutonium Exposure (Meeting Abstract). (Eng)

Weeks, R. W. (Industrial Hygiene Group, MS 486, Los Alamos Scientific Lab., P.O. Box 1663, Los Alamos, NM, 87545); Moss, W. D.; Garcia, M. C. *Health Phys* 35(6): 897; 1978. (no refs)

79-0355 Attenuation of 13-20 keV Photons in Tissue Substitutes and Their Validity for Calibration Purposes in the Assessment of Plutonium in Lungs. (Eng) Newton, D. (Environmental and Medical Sciences Div., Atomic Energy Res. Establishment, Harwell, Didcot, Oxon, England); White, D. R. *Health Phys* 35(5): 699-703; 1978.

The attenuation properties of 26 tissue substitutes for 13-20 kiloelectronvolt (keV) x-rays were compared with those of tissues encountered in the human thorax. Partial linear attenuation coefficients μ (for Compton scattering) and μ (for photoelectric interactions) were evaluated at 13.6, 17.2 and 20.2 keV. The selection of tissue substitutes that are valid for 13-20 keV radiation is predominantly a matter of matching photoelectric attenuation coefficients; Compton scattering is a relatively unimportant process of attenuation. Materials were deemed to be valid substitutes for the soft tissues of the chest wall (muscle, adipose tissue, breast, cartilage) if μ was correct to within 3% at 17.2 keV and to within 5% at 13.6 keV and 20.2 keV. The same criterion was adopted for liver and heart, even though it is probably unduly restrictive. On this basis, substitute materials for the various tissues in the human thorax are suggested, eg, Perspex (assumed to be polymethyl methacrylate) for breast tissue, latex (foamed) for liver, and polyurethane plus 4.3% calcium carbonate for heart. None of the materials examined provided a close match for the attenuation data of bone marrow. This comparison also indicated that certain substitutes used in various assessments of plutonium in the lung have been inappropriate and that the use of Alderson lung substitute contributed substantially to errors made in estimating paladium-103 in vivo. (38 refs)

79-0356 Comparison of Plutonium Distribution and Radiation Dose Received by Mouse and Dog Testis (Meeting Abstract). (Eng) Russell, J. J. (Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL, 60439); Lindenbaum, A.; Grahn, D. *Health Phys* 35(6): 895; 1978. (no refs)

79-0357 Late Effects of Inhaled Plutonium Oxide in Dogs (Meeting Abstract). (Eng) Park, J. F. (Biology Dept., Battelle, Pacific Northwest Lab., Richland, WA, 99352); Bair, W. J.; Catt, D. L.; Craig, D. K.; Dagle, J. E.; Renne, R. A.; Ragan, H. A. *Health Phys* 35(6): 888-889; 1978. (no refs)

79-0358 Primary Immune Response in Dogs Exposed to $^{239}\text{PuO}_2$ (Meeting Abstract). (Eng) Graham, T.

M. (Biology Dept., Battelle, Pacific Northwest Lab., Richland, WA, 99352); Morris, J. E. *Health Phys* 35(6): 888; 1978. (no refs)

79-0359 Distribution of ^{238}Pu in Tissues of Fish from the Canal in Miamisburg, Ohio. (Eng) Kennedy, C. W. (Ecological Sciences Section, Radiological and Environmental Res. Div., Argonne Natl. Lab., Argonne, IL, 60439); Bartelt, G. E. *Environ Res* 17(2): 228-235; 1978.

^{238}Pu concentrations were determined in the tissues of seven species of freshwater fish taken from the abandoned Miami-Erie canal in Miamisburg, Ohio. The canal contained elevated ^{238}Pu levels as a result of a spill from a Pu fabrication facility in 1969. Gizzard shad, black bullheads, carp, bluegills, black crappies, smallmouth bass, and largemouth bass were collected and various tissues were analyzed. Similar analyses were made of 100 hatchery bluegills artificially introduced into the canal. The mean ^{238}Pu concentration was 0.71 and 5.28 picocuries/liter in filtered canal water and suspended sediments, respectively. The highest ^{238}Pu levels were found in the gastrointestinal (GI) tracts and gills, the lowest levels in muscle. A rapid uptake of ^{238}Pu was observed for the hatchery bluegills. The high Pu concentrations in the GI tracts and gills suggest that these organs are potential uptake sites. The presence of ^{238}Pu in liver, gonads, bone, and muscle indicates that ^{238}Pu is translocated from the uptake sites. The high Pu concentrations in liver and increased concentrations in the bodies and GI tracts of the hatchery bluegills (which apparently were not feeding) suggest the existence of an uptake pathway other than ingestion of food and support the translocation concept. (18 refs)

79-0360 Cross Placental Transfer of Americium and Plutonium in Mice (Meeting Abstract). (Eng) Weiss, J. F. (Comparative Animal Res. Lab., Oak Ridge, TN, 37830); Walburg, H. E.; McDowell, W. J. *Health Phys* 35(6): 895-896; 1978. (no refs)

79-0361 The Comparative Distribution of Thorium and Plutonium in Human Tissues (Meeting Abstract). (Eng) Singh, N. P. (Inst. Environmental Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016); Ibrahim, S. A.; Cohen, N.; Wrenn, M. E. *Health Phys* 35(6): 897; 1978. (no refs)

79-0362 Distribution of Polonium-210 in the Human Lung (Meeting Abstract). (Eng) Cohen, B. S. (Inst. Environmental Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016); Eisenbud, M.; Wrenn, M. E.; Harley, N. H. *Health Phys* 35(6): 898; 1978. (no refs)

- 79-0363 Inhalation Carcinogenesis of High-Fired $^{244}\text{CmO}_2$ in Rats.** (Eng) Sanders, C. L. (Biology Dept., Pacific Northwest Lab., Richland, WA, 99352); Mahaffey, J. A. *Radiat Res* 76(2): 384-401; 1978.

The carcinogenicity of inhaled $^{244}\text{CmO}_2$ in the lung and bone of 277 female Wistar rats was determined. The rats were divided into five groups and exposed for 30 min to alveolar deposition levels of 0.54, 4.4, 48, 450, and 1,800 nanocuries (mCi) of ^{244}Cm . An additional 118 rats served as unexposed controls. The activity median aerodynamic diameter of the aerosol was $0.8\ \mu\text{m}$. The distribution of ^{244}Cm on autoradiograms of lung taken immediately and up to 2 yr after inhalation exposure was similar, with mostly single α tracks and only occasional α stars. Approx three-fourths of the alveolarly deposited ^{244}Cm was cleared from the lung with a half-life of 0.5 day, one-fourth with a half-life of 12 days; approx 2% was retained with a half-life of about 1 yr. ^{244}Cm uptake by bone reached a max by 50 days and who showed no change thereafter. The retention half-life of ^{244}Cm in liver and thoracic lymph nodes was < 2 wk. Rats exposed to 450 and 1,800 nCi experienced significantly increased early mortality due to radiation pneumonitis. A significant incidence of adenomatous metaplasia occurred in the 450-nCi group only; no cases of metaplasia were observed in the 1,800-nCi group. All but one of the induced lung tumors were adenocarcinomas, the exception being a squamous cell carcinoma in the 450-nCi group. Lung tumor incidence in the five respective dose groups was 1.8%, 1.7%, 13%, 32%, and 0%; no tumors occurred in controls. A significantly increased number of bone and lung tumors were found with the 48- and 450-nCi doses. On an av lung dose basis, the dose-response pattern for the induction of pulmonary adenocarcinoma from inhaled $^{244}\text{CmO}_2$ was similar to that observed for inhaled $^{239}\text{PuO}_2$, despite large differences in particle size, solubility, and alveolar clearance. (43 refs)

- 79-0364 The Retention and Distribution of ^{243}Cm and ^{244}Cm in C57BL/Do Mice.** (Eng) Smith, J. M. (Radiobiology Lab., Univ. Utah Coll. Medicine, Salt Lake City, UT, 84112); McFarland, S. S.; Calder, S. E.; Mays, C. W. *Radiat Res* 76(2): 436-440; 1978.

The whole-body retention (WBR) and tissue distribution of ^{243}Cm and ^{244}Cm were determined in 48 10-mo-old C57BL/Do mice for up to 297 days after they were inoculated with $3.5\ \mu\text{Ci/kg}$ ^{243}Cm and ^{244}Cm in 0.8 M citrate soln. The activity distribution at the time of injection was 57.6% ^{244}Cm and 42.3% ^{243}Cm . WBR was determined periodically by photon counting of the ^{243}Cm γ emission using dual 20 x 10-cm NaI(Tl) detectors. Mice were sacrificed on days 3, 14, 56, 91, and 182 postinjection, and tissue distribution of Cm in the liver, femurs, kidneys, spleen, and skeleton was determined. The WBR of ^{243}Cm and ^{244}Cm was significantly higher in males than in females, in agreement with previous studies using ^{239}Pu . Most ($> 76\%$) of the body burden of Cm was found in the liver and skeleton. From 3 to 182 days postinjec-

tion, the skeletal burden was nearly constant, averaging 25% of the injected Cm for males and 21% for females. On day 3 postinjection, the kidneys of both sexes contained 0.52% of the injected Cm, the spleen 0.02%. Further comparison of the Cm and Pu studies showed that the WBR and skeletal retention of Cm in mice of the same sex was lower than that of Pu. Hepatic retention of Cm was similar, with retained activity being higher in males. (8 refs)

- 79-0365 Dose-Response Relationships for Female Radium Dial Workers.** (Eng) Rowland, R. E. (Center Human Radiobiology, Argonne Natl. Lab., Argonne, IL, 60439); Stehney, A. F.; Lucas, H. F. *Radiat Res* 76(2): 368-383; 1978.

The probability of the separate induction of bone sarcomas and carcinomas originating in the mastoid air cells or paranasal sinuses (head carcinomas) as a function of radium dose was determined using data on 759 female radium-dial workers employed before 1930. The relative effectiveness of ^{226}Ra and ^{228}Ra and dose-incidence relationships were examined for these women, whose Ra body burden had been determined. There were 38 bone sarcomas and 17 head carcinomas in this group. Incidence was expressed as tumor cases per person-year, and the dose parameter was the quantity of Ra that entered the blood during the exposure period. Equations were fitted to the observed data for each tumor type; for each equation, the best dose-coefficient values were found by a least-squares fitting procedure. The bone sarcoma data were best described by a dose-squared exponential function, which predicts 0.24 bone sarcoma/yr among the 32 high-intake ($> 100\ \mu\text{Ci}$) surviving women and 0.006 bone sarcoma/yr among the 331 low-intake ($0.5\text{-}99\ \mu\text{Ci}$) survivors. Head carcinoma data were best described by a linear equation that predicts 0.1 case/yr for 50 surviving women exposed to $\geq 25\ \mu\text{Ci}$ and 0.02 case/yr for 294 women exposed to $0.5\text{-}24.9\ \mu\text{Ci}$. Dose-incidence equations obtained when dose was expressed as av skeletal dose in rads are also given. (28 refs)

- 79-0366 ^{222}Rn Daughter Dosimetry in the Syrian Golden Hamster Lung.** (Eng) Desrosiers, A. (Yankee Atomic Electric Co., 20 Turnpike Rd., Westboro, MA, 01581); Kennedy, A.; Little, J. B. *Health Phys* 35(5): 607-623; 1978.

Data obtained from a detailed morphometric description of the dimensions of airways, the branching patterns, and the epithelial cell frequencies in the respiratory tract of the Syrian golden hamster were used to construct a mathematical model of the deposition of inhaled particles and their subsequent regional translocation during extracellular lung clearance. Mucus velocity and particulate deposition were calculated for the trachea, for eight groups of conductive airways, and for the alveolated portion of the lung. The number of polonium (Po)-218 and ^{214}Po disintegrations per year was calculated for

each airway group using reference radon-222 (Rn)-laden atmospheres. The depth-dose distribution in the epithelial tissues of the airways was derived for each alpha particle energy. The dose to basal cells in the subsegmental bronchi is 0.4-1.6 rad per working level year (WLY). The mean dose to basal cells and Clara cells is 2.3 rad/WLY. Since Clara cells have been implicated in hamster lung carcinogenesis, the dose to these differentiated cells may be relevant to tumor induction. In contrast, models of the human lung suggest that the highest dose to all types of cells is in the higher airways (subsegmental bronchi) and that the cancer-related dose is 3-20 rad/WLY for identical ^{222}Rn -laden atmospheres. (43 refs)

79-0367 ^{226}Ra , ^{210}Pb and Calcium in Eyes of Long-Term Radium Cases (Meeting Abstract). (Eng) Holtzman, R. B. (Radiological and Environmental Res. Div., Argonne Natl. Lab., 9700 S. Cass Ave., Argonne, IL, 60439); Sha, J. Y.; Plondke, N. J. *Health Phys* 35(6): 898; 1978. (no refs)

79-0368 Factors Influencing Radiation Carcinogenesis in Bone (Meeting Abstract). (Eng) Woodard, H. Q. (Sloan-Kettering Inst. Cancer Res., New York, NY, 10021). *Health Phys* 35(6): 917; 1978. (no refs)

79-0369 Effect of Dose Distribution on the Induction of Experimental Lung Cancer by Alpha Radiation. (Eng) Little, J. B. (Dept. Physiology, Harvard Univ., Sch. Public Health, Boston, MA, 02115); Kennedy, A. R.; McGandy, R. B. *Health Phys* 35(5): 595-606; 1978.

The relative carcinogenicity of polonium-210 (^{210}Po) administered intratracheally by two different methods was studied in female Syrian golden hamsters. In one method, ^{210}Po was instilled in soluble form in a saline solution giving a uniform distribution of radioactivity throughout the lung parenchyma. In the other, Po was administered adsorbed onto ferric oxide (Fe_2O_3)-carrier particles yielding a non-uniform distribution; most of the ^{210}Po - Fe_2O_3 particles were retained in the peripheral lung, surrounding terminal and respiratory bronchioles. With lifetime doses averaged over the whole lungs of 55-2700 rad, the tumor yields for the non-uniform irradiation were less than or equal to those for uniform exposure. At low radiation doses, 9/99 animals that had received ^{210}Po alone in saline (55 rad dose) developed lung tumors while 10/75 that had received ^{210}Po - Fe_2O_3 (75 rad) developed tumors. At high radiation doses (1,500-2,700 rad), 22/38 animals that received ^{210}Po alone developed lung tumors while 39/71 that received ^{210}Po - Fe_2O_3 developed lung tumors. In the high-dose group, the life span of tumor-bearing animals was markedly reduced while there was no significant difference from controls in the low-dose groups. There was no significant differences in the histopathologic characteristics

of the tumors induced by either Po treatment. These findings indicate that the assessment of the hazards of inhaled alpha emitters using a model based on uniform distribution is a reasonable approach for radiation protection purposes. (22 refs)

79-0370 Late Effects of Inhaled $^{253}\text{Es}(\text{NO}_3)_3$ in the Rat (Meeting Abstract). (Eng) Ballou, J. E. (Biology Dept., Battelle, Pacific Northwest Lab., Richland, WA); Dagle, G. E.; Gies, R. A.; Smith, L. G. *Health Phys* 35(6): 887; 1978. (no refs)

79-0371 Lymphocytic Leukemia in Guinea Pigs Exposed to ^{85}Kr : Preliminary Report (Meeting Abstract). (Eng) Kirk, W. P. (Environmental Protection Agency, Health Effects Res. Lab., Research Triangle Park, NC, 27711); Rehnberg, B. F.; Ostby, J. S.; Wright, J. F. *Health Phys* 35(6): 889-890; 1978. (no refs)

79-0372 An Idealized Model for Translocation of Inhaled Radionuclides and Their In Vivo Produced Daughter Products (Meeting Abstract). (Eng) Langsted, J. M. (Rockwell International, Box 464, Golden, CO, 80401). *Health Phys* 35(6): 889; 1978. (no refs)

79-0373 Absence of Interaction Between X-Rays and UV Light in Inducing Ouabain- and Thioguanine-Resistant Mutants in Chinese Hamster Cells. (Eng) Cleaver, J. E. (Lab. Radiobiology, Univ. California, San Francisco, CA). *Mutat Res* 52(2): 247-253; 1978.

In an effort to detect an inducible error-prone repair system in eukaryotic cells, Chinese hamster ovary cells were sequentially irradiated with x-rays and UV light. The rationale of the protocol was that the x-rays would induce the error-prone system, and UV light would then produce more mutations than if used alone. However, no synergism was noted in the ability of the two treatments to produce ouabain or 6-thioguanine resistance in these cells, suggesting that no error-prone repair system exists. Monolayers of approx 10^6 cells were irradiated with 300 rad of x-ray, allowed to grow for up to 17 hr, and then irradiated with 13 Joule (J)/meter² (m²) of 254 nanometer UV light. Cells were kept in exponential growth for 6 days, and then incubated (5×10^5 cell/ml) with 3 mM ouabain or 0.06 mM 6-thioguanine for 7-8 days, at which time the av mutation frequencies were determined. Linear dose-response relationships were noted for both drug resistance markers independently (yields of 1.3×10^{-7} /rad and 3.6×10^{-5} /J/m² for 6-thioguanine and 1.0×10^{-6} /J/m² for ouabain); when both radiation types were applied, no synergism was noted for any time interval between irradiation treat-

ments up to 17 hr. The failure to detect a synergism of action in these treatments may indicate that the mechanisms by which mutations are produced by errors in replication and repair may be constitutive in eukaryotic cells in contrast to the inducible systems in prokaryotes. (25 refs)

- 79-0374 Induction of 6-Thioguanine- and Ouabain-resistant Mutations in Synchronized Syrian Hamster Cell Cultures During Different Periods of the S Phase.** (Eng) Tsutsui, T. (Div. Biophysics, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205); Barrett, J. C.; Ts'o, P. O. *Mutat Res* 52(2): 255-264; 1978.

The temporal replication of genes responsible for 6-thioguanine (6TG) and ouabain (OB) resistance was examined in cells of a transformed Syrian hamster line, BP6T, following synchronization, selective incorporation of 5-bromodeoxyuridine (BUdR) during specific portions of the S phase, and mutagenesis by light. The cells were synchronized by a period of growth in low serum, with subsequent blockage of the cells at the G₁/S boundary by hydroxyurea. This method provided cells with nearly 100% synchrony, although approx 20% of the cells were noncycling. The cells were then treated with 10⁻⁵ M BUdR for one of five 1-hr periods of the S phase and then irradiated with near-UV light for 5 min. BUdR + UV light induced 6TG and OB-resistant mutants, but BUdR or irradiation alone was not mutagenic. 6TG-resistant mutants were induced only during the early S phase by BUdR + UV light, but OB-resistant mutants were induced in a biphasic pattern, during early S and late S. The latter finding may indicate the presence of two genes specifying Na⁺/K⁺ ATPase that were replicated at distinct periods during S. (30 refs)

- 79-0375 Perturbations in Simian Virus 40 DNA Synthesis by Ultraviolet Light.** (Eng) Williams, J. I. (Lab. Radiobiology, Univ. California, San Francisco, CA); Cleaver, J. E. *Mutat Res* 52(3): 301-311; 1978.

The effects of UV irradiation (254 nanometers) on simian virus 40 (SV40) DNA synthesis in African green monkey kidney cells were studied during the period of max viral DNA synthesis. DNA synthesis was suppressed to 61% of control values at 20 joules (J)/m² and to 49% of control values at 40 J/m². The amount of ³H-thymidine label in Form I DNA molecules was very sensitive to UV light, whereas incorporation into replicative intermediate and Form II molecules was less sensitive, a finding consistent with inhibition of DNA chain elongation. The observed amounts of label incorporated into irradiated molecules could be predicted based on the assumption that pyrimidine dimers are responsible for blocking nascent DNA strand growth. The relative proportion of labeled Form I molecules in irradiated cultures rapidly increased to near control values with incubation after exposure to 20 or 40 J/m² of UV light (0.9-1.0 or 1.8-2.0 dimers/SV40

genome, respectively). This rapid increase and the failure of Form II molecules to accumulate suggest that SV40 growing forks can rapidly bypass many dimers. Form II molecules formed after irradiation were not converted to linear (Form III) molecules by the dimer-specific T4 endonuclease V, suggesting that there are no gaps opposite dimers in these molecules or that T4 endonuclease V cannot use Form II molecules as substrates. (41 refs)

- 79-0376 Pyrimidine Dimer Formation in Epidermal DNA and Oncogenesis in Rat Skin Exposed to Ultraviolet Radiation (Meeting Abstract).** (Eng) Strickland, P. T. (New York Univ., New York, NY, 10003). *Diss Abstr Int B* 39(6): 2691; 1978. (no refs)

- 79-0377 Contribution of a Caffeine-Sensitive Recombinational Repair Pathway to Survival and Mutagenesis in UV-irradiated *Schizosaccharomyces pombe*.** (Eng) Genter, N. E. (Biology and Health Physics Div., Atomic Energy Canada Ltd., Chalk River Nuclear Lab., Chalk River, Ontario, Canada); Werner, M. M.; Hannan, M. A.; Nasim, A. *Mol Gen Genet* 167(1): 43-49; 1978.

The role of a caffeine-sensitive recombinational process in repair of UV-induced damage in *Schizosaccharomyces pombe* was studied. G1 and G2 phase cells of wild-type *S. pombe* showed caffeine-induced lethal enhancement after UV irradiation. G1 cells were considerably more UV-sensitive than G2 cells, the resistance of the latter apparently being primarily related to the possession of a duplicated genome at the time of irradiation. The UV-sensitization by caffeine was abolished in G1 and G2 cells by the *rad1* mutation, which substantially reduces recombination following UV treatment. UV-irradiated wild-type G1 cells displayed a lag time of approx 8 hr before caffeine-sensitive repair began, and recovery was seen only after DNA synthesis had commenced. The caffeine-sensitive repair process began immediately in UV-irradiated G2 cells, however. *Rad* mutants, which show a higher UV-induced mutation rate than do wild-type cells, retained the caffeine-sensitive UV-repair process, whereas *rad* strains were relatively UV-immutable compared with the wild-type strain, which did not. The recombinational process may therefore be the major pathway responsible for UV-induced mutation in *S. pombe*. (25 refs)

- 79-0378 UV-Microirradiation of Chinese Hamster Cells and Posttreatment with Caffeine: Induction of Chromosome Shattering in Chromatin Outside the Irradiation Site (Meeting Abstract).** (Eng) Zorn, C. (Institut für Humangenetik und Anthropologie, Universität Freiburg, Freiburg, W. Germany); Cremer, T.; Cremer, C.; Zimmer, J. *Clin Genet* 14(5): 315; 1978. (4 refs)

79-0379 Induction of Chromosome Shattering by Whole Cell Irradiation ($\lambda = 254$ nm) and Posttreatment with Caffeine: A Quantitative Evaluation (Meeting Abstract). (Eng) Cremer, T. (Institut für Humangenetik und Anthropologie, Universität Freiburg, Freiburg, W. Germany); Cremer, C.; Zorn, C.; Zimmer, J. *Clin Genet* 14(5): 287; 1978. (no refs)

79-0380 The Influence of the Distribution of Photoleisions on the Induction of Chromosome Shattering in Chinese Hamster Cells by UV-Microirradiation and Caffeine (Meeting Abstract). (Eng) Cremer, C. (Institut für Humangenetik und Anthropologie, Universität Freiburg, Freiburg, W. Germany); Cremer, T.; Zorn, C.; Zimmer, J. *Clin Genet* 14(5): 286; 1978. (no refs)

79-0381 Modification of UV-induced Mutation Frequencies in Chinese Hamster Cells by Dose Fractionation, Cycloheximide and Caffeine Treatments. (Eng) Chang, C. C. (Dept. Human Development, Coll. Human Medicine, Michigan State Univ., E. Lansing, MI, 48824); D'Ambrosio, S. M.; Schultz, R.; Trosko, J. E.; Setlow, R. B. *Mutat Res* 52(2): 231-245; 1978.

Experiments were designed to determine if an inhibition of enhanced postreplication repair led to modifications in the production of UV-induced ouabain-resistant mutations in Chinese hamster V79 cells. The cells were irradiated with a fractionated dose of UV light (first dose, UV₁, 3 joules/m², followed 4-6 hr later by UV₂, 17 joules/m²). Fractionation of the UV dose always increased the colony-forming ability of these cells, but mutation frequency was either reduced or not changed. Cyclohexamide (CH) treatment (5 µg/ml) for 12 hr between irradiations reduced colony-forming ability and increased mutation frequency, whereas a 4-hr treatment between irradiations had the opposite effect. When the cells were treated with CH for 3 hr immediately after UV₁ (followed by no treatment for 3 additional hours before UV₂) reduced colony-forming ability and increased mutation frequency resulted, but when CH treatment was shifted closer in time to UV₂, this effect was diminished or even reversed. Like CH, caffeine treatment (1 mM) for 6 or 12 hr between UV treatments reduced colony-forming ability and increased mutation frequency. When added immediately after UV₁, caffeine treatment for 2, 4, and 6 hr progressively inhibited postreplication repair by UV fractionation 48%, 62%, and 100%, respectively. The results suggest that an error-free postreplication repair system exists in Chinese hamster cells that can be inhibited by particular CH or caffeine treatments. (41 refs)

79-0382 Effect of Caffeine on Ultraviolet Mutagenesis in V79 Chinese Hamster Cells. (Eng) Tatsumi,

M. (Dept. Radiation Biophysics, Kobe Univ. Sch. Medicine, Kusunoki-cho 7-12, Ikuta-ku, Kobe 650, Japan); Fujiwara, Y. *Gann* 69(5): 727-730; 1978.

The effect of caffeine on induction of 6-thioguanine-resistant (6TGr) colonies in V79 Chinese hamster cells by UV irradiation (254 nanometers) was examined by the replating method. Post-UV treatment with 1 mM caffeine had neither a synergistic nor suppressive effect on the induced 6TGr frequency, in contrast to a marked killing potentiation as a result of inhibition of replicative repair. This suggests a possible involvement of repair mechanism(s) other than replicative repair in UV mutagenesis. (25 refs)

79-0383 Ultraviolet Light Induction of Skin Carcinoma in the Mouse; Influence of cAMP Modifying Agents. (Eng) Zajdela, F. (Unité No. 22 de l'INSERM, Physiologie Cellulaire, Institut du Radium, Batiment 110, Faculté des Sciences, F 91405 Orsay, France); Latarjet, R. *Bull Cancer (Paris)* 65(3): 305-313; 1978.

A review is presented concerning the carcinogenic effect of UV irradiation on mice to introduce current experiments in which cyclic AMP (cAMP)-modifying agents were examined for their effects on UV-induced skin carcinogenesis that might result from their inhibition of DNA repair synthesis. Swiss (Carshalton) specific pathogen-free female mice were used in this study, which employed the same conditions used in previously reported studies on DNA repair inhibitors. Caffeine, theophylline, reductone (tartronic aldehyde), chloroquinone, papaverine, 3-isobutyl-1-methylxanthine (IBMX), uridine, or N-2'-O-dibutyryladenine-3'-5' cyclic monophosphoric acid (db-cAMP) were applied (40 µl of 1% or 2% soln) to one ear of a mouse before each of 133 treatments of 7.3 x 10³ Joules (J)/meter² (m²) UV irradiation (a total irradiation of 1 x 10⁶ J/m²). Whereas caffeine and theophylline reduced tumor incidence in the skin of the ear by approx 50%, reductone and chloroquinone had no effect. Likewise, uridine, a UV-absorbing compound, was also ineffective in reducing tumor number. The phosphodiesterase inhibitors IBMX and db-cAMP were not able to alter tumor yields, and papaverine, inhibited tumor yield only slightly and insignificantly (89%-73%). These results offer no support to the hypothesis that the abilities of caffeine and theophylline to inhibit tumor growth are related to their known abilities to inhibit phosphodiesterase and therefore to increase total cellular cAMP levels. The experiments do suggest that UV carcinogenesis is related to postreplication DNA repair, which favors the occurrence of errors in cellular DNA sequences. (59 refs)

79-0384 Cell Transformation by Non-Coherent Ultraviolet-Visible Light Radiation (Meeting Abstract). (Eng) Withrow, T. J. (Bureau Radiological Health, Food and Drug Admin., Dept. Health, Education and Welfare, Rockville, MD, 20857). *Health Phys* 35(6): 891; 1978. (no refs)

79-0385 DNA Repair in Human Cells Treated with Combinations of 7,12-Dimethylbenz(A)Anthracene Epoxide and Ultraviolet Radiation (Meeting Abstract). (Eng) Ahmed, F. E. (Biology Dept., Brookhaven Natl. Lab., Upton, NY, 11973); Setlow, R. B. *Biophys J* 25(2, part 2): 154a; 1979. (1 ref)

79-0386 Photodynamic Effect of Proflavine on ϕ X174 Bacteriophage, Its DNA Replicative Form and Its Isolated Single-stranded DNA: Inactivation, Mutagenesis and Repair. (Eng) Piette, J. (Lab. General and Medical Microbiology, Univ. Liege, Sart Tilman, B-4000 Liege, Belgium); Calberg-Bacq, C. M.; Van de Vorst, A. *Mol Gen Genet* 167(1): 95-103; 1978.

Repair of lesions induced by treatment with UV light plus proflavine was studied using single- and double-stranded bacteriophage ϕ X174 DNA. The infectivity of the double-stranded ϕ X replicative form (RF)I DNA was about 10-fold more sensitive to treatment with proflavine and light than was isolated ϕ X single-stranded (ss) DNA. The photodynamic inactivation of ϕ XRFI DNA appeared to be caused by intercalated dye molecules. With ϕ XRFI DNA, ϕ X ss DNA, and intact ϕ X174 phages, reactivation occurred through high multiplicities of infection and depended on the cellular rec A gene product. The pol A, uvr A, and lex A gene mutations had no effect on phage or DNA inactivation rates. The photodynamically induced lesions could be at least partially repaired by the SOS repair system induced in *Escherichia coli* host cells by irradiation with 100 Joules/meter². SOS repair did not occur in bacteria or spheroplasts irradiated in the presence of chloramphenicol. Reversion frequency of ϕ X174 amber mutations indicated that: (1) photodynamically induced lesions were mutagenic whether or not the rec A gene product was present in the indicator bacteria, (2) induction of the SOS repair system was accompanied by a mutagenic process resulting in a nearly two-fold increase in reversion frequency, and (3) multiplicity reactivation occurred through a recombinational process and was not mutagenic per se. (41 refs)

79-0387 Identification and Cytotoxic Reactivity of Inflammatory Cells Recovered from Progressing or Regressing Syngeneic UV-induced Murine Tumors. (Eng) Lill, P. H. (Dept. Pathology, Sch. Medicine, Univ. South Carolina, Columbia, SC, 29208); Fortner, G. W. *J Immunol* 121(5): 1854-1860; 1978.

The histologic appearance of tumors during progressive growth in UV-irradiated mice and during regression in normal mice was examined, and the composition and in vitro reactivity of the inflammatory cell infiltrates that could be recovered from the tumors after transplantation into these two types of recipients were compared. Syngeneic UV-induced fibrosarcomas were implanted sc bilaterally in normal

C3H/HcN(MTV-) mice (regressor animals) and in mice irradiated with 2.8 joules/m²/sec of UV light (280-340 nm) for 1 hr 3x/wk for 3-4 mo (progressor animals). At 2, 4, 6, 8, and 10 days postimplantation, tumor fragments were recovered for immunofluorescence, morphologic, and/or in vitro cytotoxicity tests. In both groups, an inflammatory filtrate of mononuclear cells and granulocytes was evident on days 2-6; by days 8-10 however, tumor cell death was evident in regressor animals, but not in UV-treated animals, whose tumors grew in size. At day 6, regressor tumors had a significantly increased lymphocyte/macrophage ratio, and immunofluorescence detected a threefold increase of T cells in regressor vs progressor tumors. Tumor lymphocytes isolated from regressor tumors at this time demonstrated significant cytotoxicity at a 1:1 effector cells:target cell ratio, but progressor lymphocytes were not cytotoxic at this ratio. Treatment of tumor cells from normal mice with anti- μ serum and complement reduced the number of T cells by 65% and cytotoxicity by 72%. Although tumor fragments were not cytotoxic before implantation, by day 4, the T-cell number in regressor tumors had increased 20 times, indicating that almost all B and T cells recovered from implanted fragments were of host origin. The inability of UV-treated mice to destroy syngeneic UV-induced tumors in vivo is apparently related to a decreased ability to mobilize T cells into the tumor and to generate cytotoxic reactivity against the tumor. (29 refs)

79-0388 An Effect of Cell-Cycle Position on Ultraviolet-Light-induced Mutagenesis in Chinese Hamster Ovary Cells. (Eng) Riddle, J. C. (Oak Ridge Graduate Sch. Biomedical Sciences, and Biology Div., Univ. Tennessee, Oak Ridge, TN, 37830); Hsie, A. W. *Mutat Res* 52(3): 409-420; 1978.

The importance of cell-cycle position in UV light-induced mutagenesis was studied using Chinese hamster ovary (CHO) cells. Populations in different stages of the cell cycle were exposed to 10 joules (J)/m². Survival decreased as the cells moved from the G₁ to the S phase, reaching a minimum 30% to 50% through the DNA synthetic period, and then rose threefold to approx 60% during the latter part of S into G₂ and mitosis. Mutation induction was generally lowest as the cells initiated DNA synthesis, rising to a max 1-2 hr into S; mitotic and very early G₁ cells appeared to be somewhat less sensitive to the mutagenic effects of UV. Fluence-response curves obtained at several times during the cell cycle yielded D_q (fluence at which the back extrapolate of the exponential portion of the curve intersects the 100% survival abscissa) values of approx 6 J/m². The primary survival characteristic that varied with cell-cycle position was D₀ (fluence required to reduce survival by a factor e⁻¹ along the exponential portion of a survival curve), which ranged from 2.5 J/m² at 6 hr after mitotic selection to 5.5 J/m² 11 hr afterward. The optimum phenotypic expression time for induced 6-thioguanine resistance was 7-9 days and was essentially independent of both UV fluence and position in the cell cycle. Hypoxan-

thine-guanine phosphoribosyltransferase activity was reduced in all mutants, but it did not differ among mutant clones that had been induced during different cell-cycle phases. Changes in cellular morphology during cell-cycle traverse did not contribute to the differential susceptibility to UV-induced mutagenesis. (40 refs)

- 79-0389 Preleukemia (Haemopoietic Dysplasia) Developing in a Patient with Psoriasis Treated with 8-Methoxypsoralen and Ultraviolet Light (PUVA Treatment).** (Eng) Wagner, J. (Medical Dept. C., Univ. Hosp., Gentofte, DK-2900 Hellerup, Denmark); Manthorpe, R.; Philip, P.; Frost, F. *Scand J Haematol* 21(4): 299-304; 1978.

The development of a preleukemic condition following treatment of psoriasis with psoralen and UV (PUVA treatment) is reported. The patient, a 73-yr-old man with psoriasis of long standing, received 8-methoxypsoralen (30 mg po) and 2 hr later skin irradiation with UV for 10-30 min (2-6 Joule/cm). The treatment was given 4 x/wk for a total of 30 wk (not consecutive). After 1 yr, he developed a preleukemic condition characterized by a refractory anemia, a slight thrombocytopenia and a normo- to hypercellular bone marrow with an excess of myeloblasts (9%-10%). Karyotyping revealed an abnormal chromosome (12P-) and agar cultures of bone marrow showed moderate growth with a high cluster/colony ratio. The patient died 1 yr later of renal failure precipitated by an acute pancreatitis. Although it is impossible to determine whether the development of preleukemia at the time of the psoralen therapy was coincidental or not, the mode of action of PUVA treatment makes it probable that the preleukemia was caused by the PUVA therapy. It is recommended that increased attention be given to the hematopoietic system of patients treated with psoralen. (19 refs)

- 79-0390 Acute Effect of 8-Methoxypsoralen and Ultraviolet Light on Sister Chromatid Exchange.** (Eng) Wulf, H. C. (Dept. Dermatology, Finsen Inst., 49 Strandboulevarden, DK-2100 Copenhagen 0, Denmark). *Arch Dermatol Res* 263(1): 37-46; 1978.

The effects of 8-methoxypsoralen (8-MOP, 10^{-6} mol/liter) and/or longwave UV light (5 or 10 joules/cm²) on the number of sister chromatid exchanges (SCE's) of normal human blood lymphocytes were studied in vitro. The number of SCE's was significantly increased in the presence of 8-MOP + ethanol (in which the 8-MOP was dissolved) without UV irradiation. Ethanol alone also caused a significant increase in SCE's. Irradiation with UV light did not increase the SCE count in the absence of 8-MOP, but irradiation + 8-MOP increased the SCE count by 50% over that seen with 8-MOP alone. UV light + 8-MOP also increased the number of banded stained chromosomes significantly. These changes were dose-dependent, and they might be responsible for the re-

duced cell turnover in psoriasis plaques seen after treatment with both agents. (33 refs)

- 79-0391 The Influence of Inhibitors on Dimer Removal and Repair of Single-Strand Breaks in Normal and Bromodeoxyuridine Substituted DNA of HeLa Cells.** (Eng) Cornelis, J. J. (Laboratoire de Biophysique et Radiobiologie, Universite Libre de Bruxelles, 67 Rue des Chevaux, 1640 Rhode St. Genese, Belgium). *Biochim Biophys Acta* 521(1): 134-143; 1978.

Paper chromatography and immunoautoradiography were utilized to monitor the time course of disappearance of pyrimidine dimers from ³H-thymidine-labeled DNA in HeLa cells irradiated with 254-nanometer UV light. Both techniques gave similar values of the extent and duration of dimer removal. Approx 100% of the removable dimers (approx 50% of all dimers) were released from the cell nuclei within 6 hr when the cells were irradiated at fluences that did not saturate the repair system. The rate of excision was constant throughout most of the cell cycle and was only arrested during mitosis. When 5-fluorodeoxyuridine (FUdR: 10^{-5} M) or 1- β -D-arabinofuranosyl cytosine (10^{-5} M) was added to the postirradiation media, excision was slowed, indicating impairment of the repair function by affecting the available deoxynucleotide pool or by inhibiting DNA polymerases, respectively. When 10% of the thymine in the DNA was replaced by bromodeoxyuridine and the cells were irradiated, the rates of dimer release and repair of single-strand breaks remained the same but occurred to a different extent. On the other hand, FUdR (10^{-5} M) and hydroxyurea (10^{-3} M) inhibited these two processes to the same degree, suggesting that some coordinated repair (perhaps common enzymes) must occur for these two lesions. (40 refs)

- 79-0392 Use of the 5-Bromodeoxyuridine-labelling Technique for Exploring Mechanisms Involved in the Formation of Chromosomal Aberrations. I. G₂ Experiments with Root-Tips of *Vicia faba*.** (Eng) Kihlman, B. A. (Dept. General Genetics, Univ. Uppsala, P.O. Box 7003, S-750 07 Uppsala 7, Sweden); Natarajan, A. T.; Andersson, H. C. *Mutat Res* 52(2): 181-198; 1978.

The ability of long-wave UV light (320-380 nanometers) and x-rays to produce aberrations in chromosomes with 5-bromouracil-substituted DNA was investigated. Chromosomes in the root-tip cells of the field bean (*Vicia faba*) were incubated with 5-bromodeoxyuridine in several schemes to produce chromosomes of the following compositions: TT-TT (both chromatids containing unsubstituted DNA), TT-TB (1 chromatid with unsubstituted DNA, 1 with unifilarly substituted DNA), TB-TB (both chromatids with unifilarly substituted DNA), and TB-BB (1 chromatid with unifilarly substituted DNA, 1 with bifilarly substituted DNA). Sister chromatids of the TT-TB and TB-TB types could be distin-

guished by differential staining. Long-wave UV light induced no aberrations in TT-TT chromosomes. In chromosomes with substituted DNA, the UV light and x-rays induced subchromatid and chromatid aberrations. Exposure of cells to UV light during G₂ produced no increase in sister chromatid exchanges (SCE), but when cells were exposed before or during S, there was a threefold increase of SCE's. Thus, SCE's are formed in connection with DNA and chromosome replication. Sensitivity to aberration production by x-rays increased with increasing number of substituted DNA strands. The increased sensitivity of TB-TB over TT-TB chromosomes was particularly striking. The question of whether a damaged chromatid may interact with an undamaged one to form an exchange was studied based on the finding that in TT-TB chromosomes, long-wave UV light produced no breaks in TT chromatids and x-rays produced about three times as many breaks in TB as in TT chromatids. The results clearly indicate that two lesions are required to produce one exchange. (27 refs)

79-0393 The Chick Embryo Chorioallantoic Membrane as a Bioassay for Angiogenesis Factors: Reactions Induced by Carrier Materials. (Eng) Jakob, W. (AdW der DDR, Institut für Wirkstofforschung, Alfred-Kowalke-Strasse 4, DDR-1136 Berlin, E. Germany); Jentzsch, K. D.; Mauersberger, B.; Heder, G. *Exp Pathol (Jena)* 15(5): 241-249; 1978.

Implantation of a variety of filter materials, sponges, and gels onto chick chorioallantoic membranes produced a local inflammatory reaction with concomitant proliferation of fibroblasts and capillaries. The initiation of the reaction was independent of the type and nature of the material and was even evoked by white eggshell membrane, coagulated albumin, and yolk. This type of vascular reaction cannot be considered characteristic of the action of a particular tumor angiogenesis factor. (17 refs)

79-0394 Cyclic Nucleotide Concentration in Colon Tissue from Wood Fiber and Asbestos Fed Rats (Meeting Abstract). (Eng) Will, L. A. (Dept. Preventive Medicine and Environmental Health, Inst. Agricultural Medicine, Univ. Iowa, Iowa City, IA, 52242); Donham, K. J.; Cole, D. A.; Stevens, R. H. *Cell Tissue Kinet* 11(6): 691; 1978. (no refs)

79-0395 The Effect of Fibre Size on the In Vitro Biological Activity of Three Types of Amphibole Asbestos. (Eng) Brown, R. C. (Medical Res. Council Pneumoconiosis Unit, Llandough Hosp., Penarth, South Glamorgan, CF6 1XW, Wales); Chamberlain, M.; Griffiths, D. M.; Timbrell, V. *Int J Cancer* 22(6): 721-727; 1978.

The effect of fiber size on the in vitro cytotoxicity of crocidolite, amosite, and anthophyllite was assessed. The three samples of amphibole asbestos were subjected to ball-milling, which reduced the length of the fibers present in each sample. The numbers of fibers in unit masses, and the distribution of fiber sizes in all the samples, both parent and milled, were estimated from electron micrographs. The ability of all samples to reduce the plating efficiency of V79-4 cells was compared, on the basis of mass, fiber number, and fiber number above various length thresholds. The biological activity of all samples correlated best with the number of fibers above a threshold length of 6.5 μ m. The toxicity of mineral fibers to V79-4 cells may prove to be a useful model in investigating the nature of the fiber/cell interactions occurring in the induction of tumors by these fibers. If the threshold length of 6.5 μ m is valid, then only about 5% of the fibers in standard (UICC) crocidolite, and 30% in amosite and anthophyllite, are active in this system. (16 refs)

79-0396 Effects of Asbestos on Epithelioid Cell Lines. (Eng) Neugut, A. I. (Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, 701 W. 168 St., New York, NY, 10032); Eisenberg, D.; Silverstein, M.; Pulk-rabek, P.; Weinstein, I. B. *Environ Res* 17(2): 256-265; 1978.

Investigation was made of the effects of asbestos on the growth and viability of two epithelioid cell lines, CHO (a malignant line derived from Chinese hamster ovary) and K-22 (a normal line derived from rat liver), and on the synthesis of plasminogen activator (PA) by these and other cell lines. Relatively low concentrations of asbestos (10 μ g/ml) were quite cytotoxic to both cell lines, with chrysotile (CT) asbestos being more toxic than crocidolite or amosite. Toxicity increased with increasing doses of chrysotile (1-10 μ g/ml). The escape, after several days, of CHO cells from CT toxicity was a consistent finding. The major and irreversible CT cytotoxicity was manifest during the first 24-48 hr of exposure. The escape may have been due to coating of the asbestos fibers by serum proteins or cellular material, or the cells may have adapted to the fibers by phenotypic cell-surface changes. The toxic factor could not be extracted from the asbestos, and toxicity occurred only if there was physical contact between fibers and K-22 and CHO cells. Although the phorbol ester tumor promoters (ie, phorbol-12-myristate acetate) induce PA synthesis in various cell cultures, asbestos did not induce this protease in epithelioid (K-22, CHO, HeLa) or chick embryo fibroblast cell cultures. Thus, PA production may not be related to the cytotoxic effects of asbestos on these cells. The cytotoxic effects of asbestos on K-22 and CHO cells were similar to those observed with macrophages and fibroblasts. It is suggested that toxicity is due to phenomena more complex than simple physical injury to the cell surface and that it may require phagocytosis. (29 refs)

79-0397 Comparison of the Lethal and Mutagenic Effects of Gold and White Fluorescent Lights on

Cultured Mammalian Cells. (Eng) Burki, H. J. (Lawrence Berkeley Lab., Univ. California, Berkeley, CA, 94720); Lam, C. K. *Mutat Res* 54(3): 373-377; 1978.

The lethal and mutagenic effects of gold and white fluorescent lights on cultured mammalian cells were compared. More than 90% of cells exposed to 6×10^4 Joules (J)/meter² (m²) white light underwent reproductive death, whereas even higher doses of gold fluorescent light (GE F30 T8 G0) were without effect. Chronic exposure of CHO cells to white fluorescent light under optimal growth conditions raised the mutation frequency by 5- to 10-fold. The effects of the white fluorescent lights were dramatically enhanced if the tops of the dishes were removed. However, exposure of cells in open dishes to gold fluorescent light caused no additional genetic effects beyond the background level of phenomena observed in darkness. Synchronized cells exposed to white light, but not to gold light, showed dramatic increases in mutants resistant to 6-thioguanine or to ouabain. The mutagenic risk to humans from usual doses of white fluorescent light is very small compared with normal mutagenic exposures received every day from the sun, and cell cultures should be shielded from daylight. (16 refs)

79-0398 Photodestruction of Pheomelanin: Role of Oxygen. (Eng) Chedekel, M. R. (Dept. Chemistry, Ohio State Univ., Columbus, OH, 43210); Smith, S. K.; Post, P. W.; Pokora, A.; Vessell, D. L. *Proc Natl Acad Sci USA* 75(11): 5395-5399; 1978.

The mechanism of the photodestruction of pheomelanin (PHM), a chromophore-protein complex from human skin and hair, was investigated. PHM was isolated from red human hair samples and subjected to photolysis under various conditions in the presence and absence of oxygen, Rose Bengal, superoxide dismutase (SD), nitroblue tetrazolium (NBT), and hydrogen peroxide. When irradiated by UV light of wavelengths longer than 300 nanometers, PHM rapidly lost color in a manner dependent upon pH and the initial concentrations of pigment and oxygen. Amino acid composi-

tion remained constant, indicating the apparent destruction of the chromophore. Photoreaction also took place in the absence of oxygen, but at a much slower rate. Photodestruction was accelerated by the singlet oxygen sensitizer Rose Bengal, and the conversion of NBT to diformazan during the photolysis of oxygenated PHM was consistent with a superoxide reaction, this conversion being quenched by the presence of SD. Hydroxyl radical produced by the dismutation of superoxide is suggested to be the primary chromophore-attacking species. These results are consistent with the involvement of superoxide in the aerobic photolysis of pheomelanin and suggest a mechanism for UV-induced cell damage in redheaded people. (40 refs)

See also:

*(Rev.): 79-0031, 79-0058, 79-0059, 79-0060, 79-0061, 79-0062, 79-0063, 79-0064, 79-0068, 79-0075, 79-0076.

*(Chem.): 79-0103, 79-0118, 79-0179, 79-0196, 79-0226, 79-0248.

*(Viral): 79-0416, 79-0417, 79-0418, 79-0459.

*(Path.): 79-0501, 79-0509, 79-0521.

*(Epid.-Biom.): 79-0557, 79-0563, 79-0564, 79-0565, 79-0566, 79-0567, 79-0568, 79-0575, 79-0583.

VIRAL CARCINOGENESIS

- 79-0399** Specific Site of Action for Single-strand Specific Nuclease on the Double-stranded Circular DNA Intermediates of an Avian RNA Tumor Virus. (Eng) Hsu, T. W. (Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA, 19111); Guntaka, R. V.; Taylor, J. M. *J Virol* 28(3): 1015-1017; 1978.

The action of the single-strand specific nuclease, S1, of *Aspergillus oryzae* on circular viral DNA intermediates obtained from the quail tumor line, QT6, at 1 day after infection was studied. S1 alone made one cut in the circles. If the circles were digested first with S1 and then with restriction endonuclease *Hpa* I, the major fragments obtained (3.25, 3.01, and 1.53 megadaltons) were indistinguishable from those obtained with *Hpa* I in the absence of S1. The specific cut with S1 did not occur if the circles were first converted to a linear form with restriction endonuclease *Kpn* I and then digested with the S1 nuclease. Also, the S1 site on the relaxed circular species was not identical to the site(s) at which the circle was nicked to become relaxed. The location of the S1 site on the circles was the same for the PrC strain of avian sarcoma virus as for the B77 strain. It is estimated that the site was in the vicinity of the tRNA (trp) primer binding site, which is immediately adjacent to but not part of the 0.21-megadalton sequence redundancy of large circular intermediates. (10 refs)

- 79-0400** Analysis of Unintegrated Avian RNA Tumor Virus Double-Stranded DNA Intermediates. (Eng) Hsu, T. W. (Inst. Cancer Res. Fox Chase Center, Philadelphia, PA, 19111); Sabran, J. L.; Mark, G. E.; Guntaka, R. V.; Taylor, J. M. *J Virol* 28(3): 810-818; 1978.

The unintegrated double-stranded avian sarcoma virus DNA intermediates that were previously detected in quail QT-6 cells at 1 day after infection were characterized. The data suggested that the unintegrated linear viral DNA intermediates synthesized in infected QT-6 cells are 0.5 ± 0.3 megadaltons (Md) larger than expected for a hypothetical unit-length double-stranded transcript of the viral RNA, excluding polyadenylic acid (A). Relative to the map restriction enzyme sites on viral DNA synthesized in vitro, the additional sequences on the in vivo-synthesized DNA seem to be located at the left end of the map and seem to represent a direct terminal redundancy of sequences located at the right side. The data also indicate that the circular DNA intermediates in the infected cells are heterogeneous in size. There are two predominant species of circle, one being about 0.21 ± 0.3 Md larger than the other. The unit-length nondefective DNA has been identified as having a mass of 5.85 Md. (24 refs)

- 79-0401** Viral Adenosine Triphosphatase. (Eng) Banerjee, R. K. (Indian Inst. Experimental Medicine,

4, Raja S.C. Mullick Rd., Calcutta-32, India). *Experientia* 34(11): 1430-1432; 1978.

The catalytic and immunological properties of an adenosine triphosphatase (ATPase) from avian myeloblastosis virus (AMV), Rous virus, and Reo virus were compared. AMV was found to hold ATPase in a conformation that induces high enzyme activity. The catalytic and antigenic properties of the Rous and AMV viruses were similar, but those of the Reo virus were significantly different. (9 refs)

- 79-0402** Primary Avian Tendon Cells in Culture: An Improved System for Understanding Malignant Transformation. (Eng) Schwarz, R. I. (Lab. Chemical Biodynamics, Lawrence Berkeley Lab., Univ. California, Berkeley, CA, 94720); Farson, D. A.; Soo, W. J.; Bissell, M. J. *J Cell Biol* 79(3): 672-679; 1978.

The in vitro transformation of highly differentiated primary avian tendon (PAT) cells by Rous sarcoma virus (RSV) was investigated. The PAT cells were grown in F12 medium with 0.2% fetal calf serum and 50 μ G/ml ascorbate. By the accepted criteria of morphologic alteration, increased rate of 2-deoxyglucose uptake, and loss of density-dependent growth control, PAT cells transformed as well as did less-differentiated chick embryo fibroblasts. The percentage of collagen produced by PAT cells following transformation by RSV decreased from 23% to 2.5%. This decrease is a function of transformation, not just of virus replication, since cells infected with a transformation-defective mutant synthesized the normal percentage of collagen. Normal PAT cells responded to the addition of ascorbate to the medium by increasing collagen synthesis from 8% to 23%. Transformed PAT cells, however, were insensitive to ascorbate, producing collagen at a level of 2.5%, with or without ascorbate addition. The normal cells also exhibited increased collagen synthesis in response to an increase in cell density, while transformed cells did not. These findings indicate that the distinctions between the normal differentiated state and the transformed state are magnified in PAT cells so that several of the virus-induced changes are easier to study. The results suggest that the breakdown in the normal regulatory mechanisms that maintain the differentiated state is related to the phenomenon of malignant transformation. (26 refs)

- 79-0403** Induction of DNA Synthesis in Terminally Differentiated Myotubes by the Activation of the *src* Gene of Rous Sarcoma Virus. (Eng) Kobayashi, N. (Dept. Microbiology, Sch. Medicine, Univ. Pennsylvania, Phila-

delphia, PA, 19104); Kaji, A. *Proc Natl Acad Sci USA* 75(11): 5501-5505; 1978.

An attempt was made to induce DNA synthesis in terminally differentiated myotubes by activating the *src* gene of Rous sarcoma virus (RSV). Mononucleated myogenic cells from 11-day-old SPAFAS chicken embryos were infected with tsLA24 or tsNY68, temperature-sensitive transformation mutants of RSV. The infected cells were then incubated at the nonpermissive temperature (41 C) and allowed to develop into multinucleated myotubes. These myotubes have withdrawn from the cell cycle, and no DNA synthesis was observed as long as the cultures were maintained at 41 C. However, when the incubation temperature was lowered to the permissive temperature (36 C) for expression of the *src* gene, DNA synthesis was induced in multinucleated myotubes. For this induction to occur, cells infected with tsLA24 had to be incubated at 36 C for at least 50 hr; cells infected with tsNY68, however, required <20 hr incubation at 36 C. Induction of DNA synthesis was observed by autoradiography as well as by measuring incorporation of ³H-thymidine into the macromolecular fraction in these myotube cultures. The constant presence of the *src* gene product is necessary for maintaining the capacity of the myotubes to induce DNA synthesis because when the temperature was returned to 41 C, this capacity was lost. During DNA induction, one biochemical marker of muscle (creatine kinase) remained unchanged. (39 refs)

- 79-0404 Immunofluorescent Detection of RNA-Dependent DNA Polymerase (Reverse Transcriptase) in XC Cells.** (Rus) Karmysheva, V. Ia. (Inst. Poliomyelitis and Virus Encephalitis, Moscow Oblast', USSR); Graevskaia, N. A.; Ivanov, A. P.; Sushko, L. N. *Dokl Akad Nauk SSSR* 242(4): 942-945; 1978.

The indirect immunofluorescent assay was employed for detection of RNA-dependent-DNA-polymerase (reverse transcriptase) in rat XC cells transformed by Rous sarcoma virus. Incubation of a cell culture with rabbit antisera against purified reverse transcriptase from avian myeloblastosis virus resulted in specific fluorescence, which was indicative of the presence of avian reverse transcriptase in the genome of XC cells. (8 refs)

- 79-0405 Chromosome Aberration in Human Neoplasm: Occurrence and Significance (Meeting Abstract).** (Eng) Levan, G. (Inst. Genetics, Univ. Gothenburg, Gothenburg, Sweden); Mitelman, F. *Clin Genet* 14(5): 300; 1978. (no refs)

- 79-0406 Comparison of the Expression of the *src* Gene of Rous Sarcoma Virus In Vitro and In Vivo.**

(Eng) Sefton, B. M. (Tumor Virology Lab., Salk Inst., San Diego, CA, 92112); Beemon, K.; Hunter, T. *J Virol* 28(3): 957-971; 1978.

The *src* gene of several strains of Rous sarcoma virus (RSV) was translated in vitro from heat-denatured 70S virion RNA in a nuclease-treated reticulocyte lysate, and the polypeptide products were compared with those present in chick cells transformed by these viruses. The in vitro translation resulted in the synthesis of several related polypeptides ranging from 17,000 to 60,000 daltons in size. When sera from tumor-bearing rats injected at birth with the Schmidt-Ruppin RSV (SR-RSV) were used for immunoprecipitation of the products of the in vitro translation of RNA from SR-RSV subgroups A and B and Prague RSV subgroup C, all but the 17,000-dalton polypeptide precipitated. The 60,000-dalton (60K) polypeptides precipitated from chick cells transformed by these viruses were essentially identical to the corresponding 60K polypeptides produced in vitro, although some strain-specific differences were evident. The precipitates from the transformed cells also contained two other polypeptides (one of 80,000 and one of approx 52,000 daltons) that were not obviously analogous to polypeptides synthesized in vitro. None of the precipitates from transformed cells contained polypeptides analogous to the 33K and 25K *src*-related in vitro products. (18 refs)

- 79-0407 Nucleotide Sequence Relationships Between the Genomes of an Endogenous and an Exogenous Avian Tumor Virus.** (Eng) Coffin, J. M. (Dept. Molecular Biology and Microbiology, Tufts Univ. Sch. Medicine, Boston, MA, 02111); Champion, M.; Chabot, F. *J Virol* 28(3): 972-991; 1978.

Oligonucleotide mapping combined with nucleic acid hybridization was used to examine and compare the genomes of Rous-associated virus-O (TRAV-O), an endogenous virus of chickens, and the Prague strain Rous sarcoma virus, subgroup B (Pr-RSV-B), an exogenous sarcoma virus. ³²P-labeled 70S RNA from each virus was digested with RNase T₁ and fingerprinted by two-dimensional gel electrophoresis which showed that the two virus genomes share large regions of identical or very similar sequence. The 5'-terminal half of the genomes (corresponding to the *gag* and *pol* regions) is virtually identical, sharing 10/13 mapped common oligonucleotides. This region is followed by a region comprising 25%-30% of the genome (the *env* region), which contains substantial nucleotide sequence differences, most or all of which are due to single base changes as judged by the results of hybridization-competition experiments combined with fingerprinting. To the 3' side of the *env* region, the RAV-O genome contains a very short sequence not found in Pr-RSV-B, whereas the Pr-RSV-B genome contains a much longer unrelated sequence. The central portion of this sequence comprises the *src* gene. The RAV-O genome does not contain any nucleotide sequence related to the "c region" found very near the 3' end of all exogenous tumor viruses.

These results imply a role for both recombination and point mutation selection events in the evolution of avian tumor virus genomes. (49 refs)

- 79-0408 Further Study on the Three-Dimensional Structure of the Core of Herpesvirus (Meeting Abstract).** (Eng) Okada, K. (Dept. Comp. Pathology, Hokkaido Univ., Sapporo, 060, Japan); Fujimoto, Y.; Nakanishi, Y. H. *J Electron Microsc* (Tokyo) 27(4): 389; 1978. (no refs)

- 79-0409 Demonstration of Mouse Mammary Tumour Virus (MuMTV) Antigenicity in Human Milk by Means of Immunodiffusion Technique.** (Eng) Zotter, S. (Institut für Pathologie, Medizinischen Akademie "Carl Gustav Carus", Fetscherstrasse 74, DDR-8019 Dresden, E. Germany); Kemmer, C.; Lossnitzer, A. *Exp Pathol (Jena)* 16(1-6): 180-185; 1978.

The micro-Ouchterlony immunodiffusion technique was used to detect mouse mammary tumor virus (MMTV) antigenicity in the 1.26- to 1.28- μ g/ml sucrose density gradient fraction of pooled human milk that had been treated with detergents and ether. The cross-reacting antigen(s) was precipitated by rabbit antisera to MMTV B particles prepared from murine milk and intracytoplasmic A particles isolated from MMT tissue. No detectable MMTV antigen(s) was seen in milk samples that had not been treated with detergent and ether. The antigen(s) seemed to be identical with the main antigenic components of murine A and B particles. Electron microscopic investigation of the human milk "core" fraction revealed abundant characteristic granular structures 40-70 nanometers in diameter that often occurred as aggregations. It is not known whether the particulate structures are indeed subviral cores and whether they are associated with the MMTV antigenicity detectable in human milk. (35 refs)

- 79-0410 Passive Immunization of Newborn RIII Mice with Antiserum to Murine Mammary Tumor Virus: Effect on Virus Expression and on Incidence of Mammary Tumors Later in Life (Meeting Abstract).** (Eng) Wald, A. (Tel Aviv Univ., Tel Aviv, Israel); Frensdorff, A. *Isr J Med Sci* 15(2): 194-195; 1979. (no refs)

- 79-0411 Naturally Occurring Humoral Immunity to Murine Mammary Tumor Virus (MuMTV) and MuMTV gp52 in Mice with Low Mammary Tumor Incidence.** (Eng) Arthur, L. O. (Viral Oncology Program, Frederick Cancer Res. Center, Frederick, MD, 21501); Fine, D. L. *Int J Cancer* 22(6): 734-740; 1978.

Antibodies to murine mammary tumor virus (MuMTV) were

found in sera from male and female mice by a radiolabeled intact MuMTV precipitation assay. These antibodies were demonstrated in strains of mice that have a high incidence of mammary tumors and transmit the highly oncogenic MuMTV via the milk (C3H) and in mice that have been foster-nursed to remove the highly oncogenic milk-borne MuMTV (C3Hf) and subsequently have a decreased mammary tumor incidence. Antibodies to MuMTV were readily demonstrated in C3H mice at 6 wk of age, whereas only marginal antibody activity was detected in C3Hf mice < 15 wk of age. Antibody levels increased the age in both strains, but in C3Hf mice the immune response was also accelerated by pregnancy. Several feral and BALB/c NIV mouse sera with high 125 I-MMTV precipitating titers also precipitated the major MuMTV envelope glycoprotein (gp52). Max precipitation of the 125 I-gp52 was > 50% with a 20% endpoint binding titer of 1:40, whereas the same sera precipitated > 80% of 125 I-MMTV with a titer of > 1:2,560. These naturally occurring antibodies were specific for gp52, since only MuMTV and purified MuMTV gp52 competed for binding of radiolabelled antigens by limiting dilutions of mouse sera. MuMTV gp52 was found in both C3H and C3Hf mice, predominantly in organs that had secretory functions, such as submaxillary glands and mammary tissue of females and submaxillary, coagulating, and vesicular glands and vas deferens of males. Extracts of other tissues were negative for MuMTV gp52. Neither gp52 nor naturally occurring antibodies for MuMTV were found in BALB/c or C57BL/6 mice. (32 refs)

- 79-0412 Mammary Tumor Virus Expression in the GR Mouse Strain: Efficiency of Chromosomal and Extrachromosomal Transmission.** (Eng) Imai, S. (Dept. Pathology, Nara Medical Univ., 840 Shijo-cho, Kashihara, Nara-ken 634, Japan); Hilgers, J.; Van Nie, R.; Verstraeten, R. *Gann* 69(5): 607-611; 1978.

Mammary tumor virus (MTV) antigen expression was determined by three different techniques in milk and secondary male genital organs of mice from segregating populations between GR and BALB/c mice: immunodiffusion tests, immunofluorescence absorption tests, and radioimmunoassay. One gene, *Mtv-2*, controls the expression of high levels of MTV antigen, as seen by the immunodiffusion test of milk and the immunofluorescence absorption test in epididymis, prostate, and coagulating glands. With the more sensitive radioimmunoassay, MTV antigens are also found in the absence of *Mtv-2*, which may be due to extrachromosomal transmission and a second gene, unlinked to *Mtv-2*. (26 refs)

- 79-0413 Strain-related Variation in the Interaction of Ferritin-conjugated Plant Lectins with Mouse Mammary Tumor Viruses.** (Eng) Hixson, D. C. (Res. Div., Univ. Texas System Cancer Center, Smithville, TX, 78957); Bowen, J. M.; Ohtsuki, Y.; Scanlon, M.; Dmochowski, L. *Cancer Res* 39(1): 199-206; 1979.

Ferritin-conjugated plant lectins of different saccharide specificities were used to characterize oligosaccharides present on the surface of mouse mammary tumor virus (MMTV) produced in mammary tumor cells from C3H/He/Tex, A/Dm, and RIII/Dm mice. A ferritin conjugate of wheat germ agglutinin specific for 2-acetamido-2-deoxy-D-glucopyranosyl residues (Fer-WGA) did not label C3H/He/Tex MMTV, whereas budding, immature, and mature forms of RIII/Dm MMTV and immature and mature forms of A/Dm MMTV were labeled; budding forms of A/Dm MMTV were partially labeled. C3H/He/Tex and A/Dm MMTV were labeled by a ferritin conjugate of concanavalin A specific for alpha-D-gluco- and alpha-D-mannopyranosyl residues, whereas RIII/Dm MMTV was only partially labeled. All MMTV's were labeled by a ferritin conjugate of *Ricinus communis* agglutinin I specific for D-galactopyranosyl residues. There was a dense, uniform distribution of Fer-WGA on all three strains of MMTV cells. No major antigenic differences were detected among the three strains of MMTV. The results suggest the existence of strain-related variations in MMTV envelope oligosaccharide determinants, and they indicate that virus-specific oligosaccharide determinants are present in cellular plasma membranes in the early stages of virus assembly. (25 refs)

- 79-0414 Detection of Mouse Mammary Tumor Virus RNA in BALB/c Tumor Cell Lines of Nonviral Etiologies.** (Eng) Dudley, J. P. (Dept. Microbiology, Univ. California Sch. Medicine, San Francisco, CA, 94143); Butel, J. S.; Socher, S. H.; Rosen, J. M. *J Virol* 28(3): 743-752; 1978.

A complementary DNA (cDNA) probe to mouse mammary tumor virus (MMTV) RNA was synthesized using calf thymus DNA oligonucleotides as a random primer. This probe was then used to study the expression of MMTV RNA in cell lines from BALB/c tumors induced in vivo either spontaneously or in response to viral, chemical, or hormonal stimuli. The cDNA had a length of approx 400-500 nucleotides and specifically hybridized to MMTV RNA and BALB/c lactating mammary gland RNA, but not to Moloney leukemia virus RNA. Calf thymus DNA-primed cDNA could protect 50% of iodinated MMTV RNA from S1 nuclease digestion at cDNA-RNA ratios of 1:1 and 90% of labeled viral RNA at ratios of 10:1. Thermal denaturation of MMTV RNA-cDNA hybrids yielded a T_m of 88.5 C, indicative of a well-base-paired duplex. Screening of mouse mammary tumor cells from MMTV sequences revealed that 3/5 lines of BALB/c origin had undetectable levels of viral RNA (<3 molecules/cell) by RNA excess hybridization. Two of the three "virus-negative" cell lines were derived from tumors induced by 7,12-dimethylbenz(a)anthracene, whereas the third tumor occurred spontaneously. Two lines from tumors induced by either viral (mammary tumor virus) or hormonal (17- β -estradiol) stimulus contained between three and nine molecules of MMTV RNA per cell by both RNA excess and cDNA excess hybridization. Clonal derivatives of these

tumor lines had levels of viral RNA comparable to those of their parental lines. Therefore, it appears that the presence of detectable MMTV RNA sequences is not a necessary requirement for the maintenance of all murine mammary gland neoplasias. (35 refs)

- 79-0415 Isolation of Host-Range Variants of Mouse Mammary Tumor Viruses That Efficiently Infect Cells In Vitro.** (Eng) Howard, D. K. (Lab. Viral Carcinogenesis, NCI, NIH, Building 37, Room 1B19, Bethesda, MD, 20014); Schlom, J. *Proc Natl Acad Sci USA* 75(11): 5718-5722; 1978.

Host-range variants of the highly oncogenic mouse mammary tumor virus (MMTV) of RIII, C3H, and GR mice were isolated. These variants have the ability to productively infect cells in vitro with high efficiency (at multiplicities of infection ≤ 1) and with extremely short latent periods to the production of de novo virus (within 4 days after infection). The variants were obtained by serial virus passage in feline cells. The resultant variant stocks reacted in group-specific radioimmunoassays for the MMTV major external glycoprotein (gp52) and major internal protein (p28), possess a protein profile similar to that of wild-type MMTV, and contain a virion-associated DNA polymerase with a magnesium cation preference. Addition of dexamethasone and insulin to culture media enhanced the titer of de novo MMTV to levels of approx 10^{10} particles per 75-cm² flask (containing 5×10^6 cells) per 24 hr. Variant stocks exhibited no evidence of contamination with either murine or feline C-type retroviruses. MMTV variants derived from C3H and RIII mice exhibited differential host ranges that included the ability to productively infect feline, canine, bat, mink, murine, and human cells. These MMTV host-range variants will facilitate study of the complete replicative cycle of MMTV and elucidate the interaction of MMTV with various hormones, physical or chemical carcinogens, and tumor promoters in the initiation and promotion of mammary neoplasia. (20 refs)

- 79-0416 The Role of Prothymocytes and the Thymic Microenvironment in Pathogenesis of Thymic Lymphomas (Meeting Abstract).** (Eng) Waksal, S. D. (Tufts Cancer Res. Center, Tufts Univ. Sch. Medicine, Boston, MA, 02111). In: *Program and Abstracts of the 12th International Leukocyte Culture Conference held in Beer Sheva, 25-30 June, 1978*. Ben Gurion University of the Negev. (Beer Sheva, Israel): 347 pp.; p. 81; 1978. (no refs)

- 79-0417 Specificity of Cell Surface Virus Receptors on Radiation Leukemia Virus and Radiation-induced Thymic Lymphomas.** (Eng) McGrath, M. S. (Lab. Experimental Oncology, Dept. Pathology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305); Decleve, A.; Lieberman,

M.; Kaplan, H. S.; Weissman, I. L. *J Virol* 28(3): 819-827; 1978.

The fluorescence-activated cell sorter was used to quantitate the binding of fluorescent C57BL/Ka retrovirus isolates to mouse lymphoid cells. The binding to fluoresceinated or rhodaminated murine leukemia virus (MuLV) to target cells showed saturation kinetics and was blocked by homologous MuLV; bound MuLV had a polypeptide profile identical to that of input MuLV. Thymic lymphomas bound specifically the MuLV that induced them, whereas only 0.5% to 2% of normal thymocytes showed equivalent MuLV binding. Simultaneous binding of excess fluoresceinated radiation leukemia virus (RadLV) and rhodaminated MCF-247 AKR virus to RadLV-induced and spontaneous AKR thymic lymphomas indicated that each lymphoma possessed receptors that could distinguish and preferentially bind the inducing virus. RadLV-induced thymic lymphomas bound only thymotropic-leukemogenic RadLV and not eco- or xenofibrotropic MuLVs. Thus, virus binding in this system involves only leukemogenic isolates of these retroviruses, implying a central role of this receptor-ligand interaction in the processes of leukemic transformation. (21 refs)

79-0418 Two Independent Genes Control the Generation of T Killer Lymphocytes in the Syngeneic RL o 1 Tumor System (Meeting Abstract). (Eng) Duprez, V. (Laboratoire d'Immunologie et Virologie des Tumeurs, U. 152 INSERM, Hopital Cochin, Paris, France); Gomard, E.; Levy, J. P. In: *Program and Abstracts of the 12th International Leukocyte Culture Conference held in Beer Sheba, 25-30 June, 1978*. Ben Gurion University of the Negev. (Beer Sheba, Israel): 347 pp.; p. 19; 1978. (no refs)

79-0419 Effect of the H-2 Complex on Sensitivity to Viral Leukemogenesis in Mice (Meeting Abstract). (Eng) Lonai, P. (Weizmann Inst. Science, Rehovot, Israel); Haran-Ghera, N. *Isr J Med Sci* 15(2): 186; 1979. (no refs)

79-0420 Phagocytic Thymus Epithelial Reticulum Cells: A Favorable Site for Leukemic Cell Proliferation (Meeting Abstract). (Eng) Peled, A. (Weizmann Inst. Science, Rehovot, Israel); Haran-Ghera, N. *Isr J Med Sci* 15(2): 187; 1979. (no refs)

79-0421 Genetic, Endocrine, and Immunological Aspects of the Prelymphomatous AKR Mouse (Meeting Abstract). (Eng) Vriend, J. (Univ. Texas Health Science Center, San Antonio, TX, 78229). *Diss Abstr Int B* 39(6): 2630; 1978. (no refs)

79-0422 Infectious Murine Leukemia Virus from DNA of Virus-negative AKR Mouse Embryo Cells. (Eng) Lowy, D. R. (Dermatology Branch, NCI, NIH, Bethesda, MD, 20014). *Proc Natl Acad Sci USA* 75(11): 5539-5543; 1978.

The infectivity of AKR DNA was determined in experiments in which (1) the AKR cells from which the transfecting DNA was isolated or (2) the NIH 3T3 cells onto which the transfecting DNA was inoculated were treated with 20 or 100 µg/ml 5-iododeoxyuridine (IUdR). DNA from virus-negative AKR mouse embryo cells was infectious for NIH 3T3 cells if the transfected cells were treated with IUdR 24 hr before and/or after addition of the DNA. The virus isolated after transfection of the AKR DNA was an ecotropic murine leukemia virus (MuLV) indistinguishable from endogenous AKR MuLV. The AKR DNA was not infectious in the absence of IUdR treatment of the recipient cells. DNA from AKR cells treated with IUdR before DNA was not infectious unless the recipient cells had been treated with IUdR. Transfected DNA from NIH mouse cells was not infectious even when the recipient cells had been treated with IUdR. DNA from cells chronically infected with AKR MuLV or Rauscher MuLV was infectious with or without IUdR treatment of the recipient cells, but the infectivity was not enhanced by IUdR. The results indicate that the endogenous AKR MuLV DNA genome is potentially infectious. The data are consistent with an IUdR-sensitive restriction in the recipient NIH 3T3 cells that prevents viral replication from endogenous AKR MuLV DNA but does not prevent viral replication from MuLV DNA of productively infected cells. (44 refs)

79-0423 Modulation of Endogenous Retrovirus Antigens on the Surface of T Lymphocyte-derived L5178Y Lymphoma Cells in Mice with L5178Y Dormant Tumors (Meeting Abstract). (Eng) Wheelock, E. F. (Dept. Microbiology, Thomas Jefferson Univ., Philadelphia, PA, 19107); Weinhold, K. J.; Genovesi, E.; Marx, P. A. In: *Program and Abstracts of the 12th International Leukocyte Culture Conference held in Beer Sheba, 25-30 June, 1978*. Ben Gurion University of the Negev. (Beer Sheba, Israel): 347 pp.; p. 83; 1978. (no refs)

79-0424 Observations of Virion Budding in Cultivated Leukemic Lymphoblasts by Means of Scanning Electron Microscopy (Meeting Abstract). (Eng) Matsumoto, A. (Dept. Microbiology, Sch. Medicine, Kawasaki Univ., Okayama, Japan). *J Electron Microsc (Tokyo)* 27(4): 359; 1978. (no refs)

79-0425 Characterization of Rauscher Murine Leukemia Virus Envelope Glycoprotein Receptor in

Membranes from Murine Fibroblasts. (Eng) Kalyanaraman, V. S. (Dept. Cell Biology, Litton Bionetics, Inc., Bethesda, MD, 20014); Sarngadharan, M. G.; Gallo, R. C. *J Virol* 28(3): 686-696; 1978.

The nature of the murine cell-surface receptor for Rauscher murine leukemia virus (R-MuLV) was analyzed. Plasma membrane preparations from KA31 (mouse) cells contained receptors for the binding of the R-MuLV envelope glycoprotein gp70. This binding was demonstrated by gel filtration of a mixture of the microsomal fraction of the cells and ¹²⁵I-labeled gp70. A rapid and convenient assay was developed to measure the complex formation between the membrane receptors and gp70. It involved specific precipitation of the complex by 3% to 4% polyethylene glycol. Complex formation was responsive to the concentrations of both the receptor and gp70 and also to changes in temperature and pH. gp70 binding was a noncooperative, saturable process, and an association constant of $3.5 \times 10^8 \text{ M}^{-1}$ was estimated from the binding data. The complex formation was reversible, and a near-total exchange of ¹²⁵I-labeled gp70 in the complex was achieved by incubation with excess unlabeled gp70. Complex formation was inhibited by protein-denaturing agents, guanidine hydrochloride, and urea. Pretreatment of the membrane fractions with chymotrypsin or phospholipase C led to a loss of the membrane-associated receptor activity, indicating that a lipoprotein structure was important for receptor function, consistent with the observation that non-ionic detergents strongly inhibit complex formation. (32 refs)

79-0426 Tryptic Peptide Analyses of Polypeptides Generated by Premature Termination of Cell-free Protein Synthesis Allow a Determination of the Rauscher Leukemia Virus *gag* Gene Order. (Eng) Murphy, E. C. (Biology Dept., Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Arlinghaus, R. B. *J Virol* 28(3): 929-935; 1978.

Polypeptides thought to be fragments of the Rauscher murine leukemia virus (R-MuLV) *gag* precursor (Pr65*gag*) were studied by tryptic peptide analysis and the results were used to determine the R-MuLV *gag* gene order. Translation of R-MuLV 35S RNA in an mRNA-dependent cell-free protein-synthesizing system yielded polypeptides identical to authentic Pr65*gag* and *gag-pol* precursor (Pr200*gag-pol*) as well as premature termination fragments of mol wt 40,000, 33,000, 28,000 (which migrated as a doublet at 27,000 and 28,000 mol wt in polyacrylamide gels), and 18,000 (designated P40*gag*, P33*gag*, P27/28*gag*, and P18*gag*, respectively). The tryptic maps of these premature termination polypeptides were compared with that of full-size Pr65*gag*. The data indicated that in comparison with Pr65*gag*, P40*gag* was missing all of protein p10 and part of protein p30, placing p10 at the C terminus of Pr65*gag* and p30 next to it. Both P33*gag* and P27/28*gag* appeared to contain all of protein p15 and protein p12 but progressively lesser amounts of p30. In comparison with p27/28*gag*, P18*gag* had lost the p12 tryptic pep-

tide. The results suggest that the R-MuLV *gag* gene order is NH₂-p15-p12-p30-p10-COOH. (18 refs)

79-0427 Changes in Splenic Cell Size Distribution During Murine Viral Leukemogenesis (Meeting Abstract). (Eng) Meredith, R. F. (Cancer Res. Unit, Allegheny General Hosp., Pittsburgh, PA, 15212); Campagna, E. D.; Mager, J. G.; O'Kunewick, J. P. *Cell Tissue Kinet* 11(6): 685; 1978. (no refs)

79-0428 Low-Multiplicity Infection of Moloney Murine Leukemia Virus in Mouse Cells: Effect on Number of Viral DNA Copies and Virus Production in Producer Cells. (Eng) Fan, H. (Tumor Virology Lab., Salk Inst., San Diego, CA, 92112); Jaenisch, R.; MacIsaac, P. *J Virol* 28(3): 802-809; 1978.

NIH-3T3 and SV-T2 mouse cells infected with Moloney murine leukemia virus (M-MuLV) were cloned using two different methods, and the number of M-MuLV-specific DNA copies per infected cell was determined. The number of M-MuLV-specific DNA copies detected varied from one to eight per infected cell in different lines. All cultures prepared by the multiple cycle of infection method had more than two copies of M-MuLV per diploid cell equivalent, whereas 8 of the 13 cultures prepared by the low multiplicity of infection method had less than two copies per diploid cell equivalent. However, some of the latter cultures contained as much or more viral DNA than did cultures prepared by the former method. A strict gene-dosage effect on virus production was not observed, indicating that other regulatory mechanisms affecting the amount of virus production must exist. The data indicate that infection at low multiplicity followed by cloning of individual cells before virus spread has occurred can result in infected cells that contain only one copy of M-MuLV-specific DNA. (22 refs)

79-0429 Structure of the Murine Leukemia Virus Reverse Transcriptase (Meeting Abstract). (Eng) Panet, A. (Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel); Tal, B.; Berliner, H. *Isr J Med Sci* 15(1): 103; 1979. (no refs)

79-0430 Major Histocompatibility Complex Involvement in Moloney Virus-induced Leukemogenesis (Meeting Abstract). (Eng) Debre, P. (Laboratoire d'Immunologie et Virologie des Tumeurs, INSERM-U. 152, Hopital Cochin, Paris, France); Gisselbrecht, S.; Blaineau, C.; Bismuth, A.; Levy, J. P. In: *Program and Abstracts of the 12th International Leukocyte Culture Conference held in Beer*

Sheba, 25-30 June, 1978. Ben Gurion University of the Negev. (Beer Sheva, Israel): 347 pp.; p. 16; 1978. (no refs)

79-0431 The Influence of α -Fetoprotein on Moloney Sarcoma Virus Oncogenesis: Evidence for Generation of Antigen Nonspecific Suppressor T Cells. (Eng) Gershwin, M. E. (Section Rheumatology-Clinical Immunology, Univ. California Sch. Medicine, Davis, CA); Castles, J. J.; Ahmed, A.; Makishima, R. *J Immunol* 161(6): 2292-2298; 1978.

A study was made of the effect of murine α -fetoprotein (AFP) on the threshold dose, mean tumor size, regression time, and number of progressors for Moloney sarcoma virus (MSV)-induced tumors in BALB/c mice. AFP-treated mice (200 μ g ip) developed larger tumors, required a longer period for regression, and had a significantly higher mortality than murine albumin treated mice (200 μ g ip). Furthermore, AFP, but not murine albumin or transferrin, allowed tumor growth when normally subthreshold doses of virus were injected. These effects of AFP could be removed by pretreatment and precipitation of AFP by anti-AFP; on the other hand, they were not altered by dialysis and were noted at serum levels of approx 170 to 440 μ g/ml. The heightened susceptibility of AFP-treated mice to MSV appears to be due to the generation of a cortisone- and radiation-sensitive splenic, and not lymph node, suppressor T cell. Indeed, the suppression produced by AFP was antigen-nonspecific and could be demonstrated in unmanipulated mice after transfer of spleen cells from AFP-treated donors. This transfer of suppression was noted in the IgG and IgA secondary responses to sheep RBC as well as by quantitating the response of T cell mitogens on spleen cells. These data suggest that AFP, in pharmacologic doses, alters a subpopulation of spleen cells to exhibit suppressive function or that AFP is involved in differential homing patterns of lymphoid cells. The relationships of AFP and immune competence appear to be broad. (36 refs)

79-0432 Retinoids Block Phenotypic Cell Transformation Produced by Sarcoma Growth Factor. (Eng) Todaro, G. J. (NCI, NIH, Bethesda, MD, 20014); De Larco, J. E.; Sporn, M. B. *Nature* 276(5685): 272-274; 1978.

The effects of retinoids on sarcoma growth factor (SGF)-induced transformation and growth of rat fibroblast cells (NRK) in culture were studied. Retinyl acetate (6 nanograms/ml) inhibited the transforming effect and almost abolished the growth-stimulatory effect of SGF but did not affect normal growth properties. Neither retinyl acetate nor retinoic acid reversed the phenotype of virally transformed cells nor blocked cell transformation produced by the Moloney strain of mouse sarcoma virus (MSV) or simian virus 40. Retinoids prevented SGF-induced colony formation in soft agar but did not inhibit the growth of MSV-transformed mouse and rat cells in soft agar. The data suggest that endoge-

nous growth promoters may be significant factors in naturally occurring cancers and that suppressors of transformation offer a potential approach to preventing the expression of the transformed phenotype. (26 refs)

79-0433 Nucleic Acid Hybridization Employed to Characterize a Murine Myeloma C-Type Virus (Meeting Abstract). (Eng) Yaniv, A. (Sackler Sch. Medicine, Tel Aviv Univ., Tel Aviv, Israel); Gazit, A. *Isr J Med Sci* 15(1): 103-104; 1979. (no refs)

79-0434 Feline Sarcoma Virus Induced Sarcomas in Neonatal Lambs: Further Studies. (Eng) Anderson, B. C. (Univ. California, Davis, CA, 95616). *Diss Abstr Int B* 39(6): 2692; 1978. (no refs)

79-0435 Complement and Tumor Antibody Levels in Cats, and Changes Associated with Natural Feline Leukemia Virus Infection and Malignant Disease. (Eng) Grant, C. K. (Dept. Microbiology, Harvard Sch. Public Health, Boston, MA, 02115); Pickard, D. K.; Ramaika, C.; Madewell, B. R.; Essex, M. *Cancer Res* 39(1): 75-81; 1979.

Lytic complement and complement-dependent antibody (CDA) levels were measured in 314 normal and feline leukemia virus (FeLV)-infected cats. None of 11 specific-pathogen-free (SPF) cats showed evidence of FeLV infection or CDA in the blood, and of 191 non-SPF cats that were negative for FeLV infection, 99 were also negative for CDA. Greatly depleted complement levels were detected only in cats that were FeLV- or CDA-positive. Of 15 laboratory cats bled periodically, CDA titers tended toward a slight loss of activity with time in the 9 that remained free of FeLV infection; CDA activity showed a minor cycling effect in the 6 animals that were persistently viremic. Complement levels remained relatively constant in the FeLV-negative animals, but fluctuated considerably in the FeLV-positive cats. Severely depleted complement levels were sometimes associated with FeLV-related anemia or lymphoid cancers. The data suggest that CDA may protect cats from developing FeLV-related leukemias or lymphomas. It is possible that some lymphoid tumors in cats develop and progress in the face of a CDA-mediated tumor immune response at times when complement levels are depleted. (36 refs)

79-0436 Surface Antibodies of Human Myelogenous Leukaemia Leukocytes Reactive with Specific Type-C Viral Reverse Transcriptases. (Eng) Jacquemin, P. C. (Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20014); Saxinger, C.; Gallo, R. C. *Nature* 276(5685): 230-236; 1978.

An attempt was made to determine whether antibodies (ab's) to specific reverse transcriptases (RT's) from certain mammalian C-type oncornaviruses can be identified in humans. Purified IgG from acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML) or normal blood WBC was tested for inhibition of various viral RT's. Purified IgG from the CML patients in blast crisis (CML-BC) specifically neutralized RT from feline leukemia virus, but purified IgG from the AML patients and from normal subjects were less reactive and, in some cases, preferentially reacted with the RT from horizontally transmitted primate C-type viruses. This indicates the presence of a heterogeneous immune response to RT or to an RT-like molecule in humans. Evidence that the inhibitor of RT in eluates from some human WBC is a specific ab and that the reaction is an antigen-ab interaction includes the biochemical and physical properties of the most reactive fraction, the specificity of the inhibition of polymerization reactions, the removal of known nonspecific inhibitors of these reactions, and assays based on factors other than inhibition of enzyme activity. The presence of an ab with relatively high activity and specificity to FeLV RT in CML-BC and the absence of IgG with similar anti-RT specificity in the chronic phase and remission of CML and in randomly selected normal blood samples might help in detecting early blast transformation in this disease. Similarly, the preferred reactivity of the IgG from AML WBC against RT from simian sarcoma virus and the preferred reactivity of the IgG from normal blood WBC against RT from gibbon ape leukemia virus may be useful in following patients in remission and in preleukemic states. (49 refs)

- 79-0437 Effect of RNA Tumor Virus-specific Protein p30 on Reverse Transcriptase. Intraspecies and Interspecies Interaction Between Reverse Transcriptase and p30.** (Eng) Bandyopadhyay, A. K. (Lab. Molecular Biology, Baltimore Cancer Res. Center, NCI, NIH, Baltimore, MD, 21201); Levy, C. C. *J Biol Chem* 253(22): 8285-8290; 1978.

The intra- and interspecies interaction between the reverse transcriptase (RT) and p30 purified from various retroviruses was examined. RT and p30 from feline leukemia virus, simian sarcoma virus, endogenous rat virus, and rhabdomyosarcoma virus formed multiprotein complexes between both intra- and interspecific sources. Intraspecific complexes stimulated the incorporation of ³H-thymidine monophosphate into (dT)₁₂(rA)_n several times over that produced by RT alone. Interspecific complexes also increased incorporation, but to a lesser extent. The molar ratios of p30:RT necessary for max enzyme activity were 30-35:1 for autologous proteins, 40-60:1 for heterologous proteins. The sedimentation rate value of the intraspecies complexes varied between 12S and 16S, and Sepharose gel filtration indicated that the mol wt of these complexes was approx 400,000; values for the interspecies complexes were 18S and 600,000. KCl dissociated all complexes into individual RT and p30 components, although the concentration required was much lower for the interspecies complexes (0.3 vs 0.8 M KCl). Competition studies in which an

interspecies complex was exposed to p30 autologous to the RT within the complex resulted in displacement of the heterologous (p30) protein and the formation of a new intraspecific complex. (22 refs)

- 79-0438 Bovine Leukosis: Investigation of Risk for Man.** (Eng) Olson, C. (Dept. Veterinary Science, Univ. Wisconsin, Madison, WI, 53706); Driscoll, D. M. *J Am Vet Med Assoc* 173(11): 1470-1472; 1978.

To evaluate previous comparative studies that failed to show a positive correlation between human and bovine leukosis and to evaluate the risk of bovine leukosis virus (BLV) infection for man, an attempt was made to detect antigens of BLV in human peripheral blood lymphocytes cultured from the blood samples of 50 volunteers with varying degrees of exposure to BLV and to cattle. Blood samples underwent analysis by fluorescent antibody tests, immunodiffusion (ID), and single radial ID tests. Results revealed that all 50 volunteers were negative for antibody to both p23 and glycoprotein BLV antigens. Since it appears that human beings probably exposed to BLV do not develop detectable antibodies to the virus, it is concluded that there is no relation between bovine leukosis and human leukemia. Although a possible association between these entities was indicated by a few preliminary studies, strong statistical evidence supports the hypothesis that BLV is not oncogenic for humans. (24 refs)

- 79-0439 Epidermodysplasia Verruciformis: Viral Particles in Early Malignant Lesions.** (Eng) Yabe, Y. (Dept. Virology, Cancer Inst., Okayama Univ. Medical Sch., Okayama 700, Japan); Yasui, M.; Yoshino, N.; Fujiwara, T.; Ohkuma, N.; Nohara, N. *J Invest Dermatol* 71(4): 225-228; 1978.

The lesions in two patients with Epidermodysplasia verruciformis (EV) were examined histologically and by electron microscopy. Four of the lesions showed the benign histologic appearance typical of EV. In all four lesions viral particles which appeared to belong to the papova group were observed. These particles were generally found in the cell nuclei and frequently showed crystalline arrangements. Virus particles resembling the virus of common human warts were also found in these lesions. A fifth lesion appeared histologically to be in an early stage of malignant transformation (intraepidermal epithelioma) and a sixth appeared to be in a more advanced stage of transformation (early invasive squamous cell carcinoma). Viral particles of the same size and morphology as those found in the benign lesions were found in these lesions also, but the number of particles per cell was less than in the benign lesions. The results suggest that at least some of the virus-induced lesions of EV actually become malignant. (17 refs)

- 79-0440 Extent of Transcription of the E Strand of Polyoma Virus DNA During the Early Phase**

of Productive Infection. (Eng) Acheson, N. H. (Dept. Virology, Swiss Inst. Experimental Cancer Res., 1066 Epalinges, Switzerland); Mieville, F. *J Virol* 28(3): 885-894; 1978.

The extent of transcription of the E strand of polyoma virus DNA during early infection was determined by a method in which the relative rate of synthesis of RNA from coding and noncoding regions of the E strand could be measured directly. Early polyoma virus-specific RNA, in nuclei and cytoplasm of mouse kidney cells pulse-labeled with ³H-uridine, was analyzed by hybridization with filter-bound *Hpa*II fragments of polyoma DNA. About 40% of labeled cytoplasmic virus-specific RNA hybridized with *Hpa*II fragment 2, which represents about 40% of the region coding for E-strand messenger RNA's (mRNA's); <5% hybridized with fragments 1 or 3, which lie outside this region. About 30% of labeled nuclear virus-specific RNA hybridized with fragment 2, and a small but significant fraction (7% to 14%) hybridized with fragments 1 and 3. About two-thirds of the nuclear RNA that hybridized to fragment 1 was complementary to the E strand, and one-third was complementary to the L strand. Results did not vary greatly in samples labeled for 15 min to 3 hr. The major species of pulse-labeled nuclear polyoma-specific RNA sedimented at 22S and thus is slightly larger than the 19S cytoplasmic mRNA. These results show that approx 75% of early nuclear RNA is transcribed from the region of the E strand, which codes for early mRNA's, and that there is probably a site at which transcription is terminated at the end of this region. However, approx 15% of early nuclear RNA is transcribed from the remainder of the E strand, perhaps by readthrough of this termination signal. In addition, there is a small amount of transcription from the L strand, whose significance is unclear. Neither the L-strand transcripts nor the nonmessenger E-strand transcripts are transported to the cytoplasm. (40 refs)

- 79-0441 Sequences from the Genome of a Non-transforming Mutant of Polyoma Virus. (Eng) Soeda, E. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2, England); Griffin, B. E. *Nature* 276(5685): 294-298; 1978.

The region of the polyoma virus DNA that probably determines the nontransforming phenotype of *hr-t* mutant NG-18 was sequenced and compared with wild-type polyoma virus DNA. NG-18 was previously shown to have a deletion of about 3% that mapped at 80-85 units on the physical map of wild-type polyoma virus DNA. The present study indicated that the fifth largest *Hinf* I restriction endonuclease fragment in polyoma DNA contained the NG-18 deletion. Except for this deletion, the mutant and wild-type DNA's were indistinguishable over this region, suggesting that the deletion is responsible for the mutant phenotype. Any protein(s) induced by the mutant would likely be smaller than might be expected from a consideration of the size of the deletion alone, and a protein from NG-18 would probably lack most of the cysteines contained in the translation product from

wild-type DNA. The region of the DNA covered by the deletion is probably not a coding region for large tumor (T) antigen. However, the sequences that lie between 80.5 and 84 units on the physical map of polyoma virus DNA probably code for a part of small t antigen and may also code for the membrane-associated protein reported for polyoma virus. Both small t antigen and this protein may have a role in transformation. (29 refs)

- 79-0442 BK and Herpes Simplex Virus Antibodies in Renal Cell Carcinoma. (Eng) Pyrhonen, S. (Lab. Viral Immunopathology, Dept. Virology, Univ. Helsinki, Haartmaninkatu 3, SF-00290 Helsinki 29, Finland); Manttyjarvi, R.; Tykka, H.; Sarna, S.; Tallberg, T. *Med Biol* 56(4): 194-200; 1978.

The relationship between serum antibodies against BK virus (BKV) and postoperative clinical course was studied in 76 renal cell carcinoma patients. BKV antibodies and antibodies against seven control viruses were determined by the hemagglutination-inhibition or complement-fixation technique. BKV and herpes simplex virus (HSV), but no other virus antibodies, showed a clear correlation with the clinical course of the renal carcinomas. The patients without BKV antibodies or with marginal antibody titers (≤ 10) had a significantly longer observed expectation (OE) of life (44.1 mo) than the patients with BKV antibody titers ≥ 20 (26.7 mo). Similarly, patients with low or undetectable HSV antibodies (titer ≤ 8) also had a significantly longer OE of life (54.0 mo) than the rest of the patients (32.7 mo). The results suggest that BKV and HSV have an as yet undefined relationship to renal cell carcinomas. (39 refs)

- 79-0443 Nucleosome Structure of SV40 Chromatin (Meeting Abstract). (Eng) Oda, T. (Dept. Biochemistry, Cancer Inst., Okayama Univ. Medical Sch., Okayama, Japan); Watanabe, S.; Nakamura, T.; Hidaka, H.; Tsutsui, K.; Omura, S. *J Electron Microsc (Tokyo)* 27(4): 379-380; 1978. (no refs)

- 79-0444 Amino Acid Sensitivity in 3T3 and SV40-transformed 3T3 Cells (Meeting Abstract). (Eng) Heiser, W. C. (Univ. California, Santa Barbara, CA, 93106). *Diss Abstr Int B* 39(6): 2620; 1978. (no refs)

- 79-0445 Division of Normal and Virus-Transformed Cells in Cellular Aggregates (Meeting Abstract). (Eng) Carrino, D. A. (Case Western Reserve Univ., Cleveland, OH, 44106). *Diss Abstr Int B* 39(6): 2778-2779; 1978. (no refs)

79-0446 Mapping of m⁶A-containing Sequences of Simian Virus 40 19 S and 16 S mRNA (Meeting Abstract). (Eng) Canaani, D. (Weizmann Inst. Science, Rehovot, Israel); Lavi, S.; Groner, Y. *Isr J Med Sci* 15(1): 101; 1979. (no refs)

79-0447 Characterization and Biogenesis of Nuclear Simian Virus 40 RNA (Meeting Abstract). (Eng) Horowitz, M. (Weizmann Inst. Science, Rehovot, Israel); Laub, O.; Bratosin, S.; Reuveni, Y.; Aloni, Y. *Isr J Med Sci* 15(1): 100; 1979. (no refs)

79-0448 Comparison of Simian Virus 40 Big and Little T Antigens (Meeting Abstract). (Eng) Prives, C. (Weizmann Inst. Science, Rehovot, Israel); Shure, H.; Gidoni, D.; Beck, Y.; Oren, M. *Isr J Med Sci* 15(1): 100-101; 1979. (no refs)

79-0449 Transcription of Cellular DNA in a Cloned Host-substituted Simian Virus 40 DNA Variant (Meeting Abstract). (Eng) Hartman, J. B. (Weizmann Inst. Science, Rehovot, Israel); Laub, O.; Aloni, Y.; Winocour, E. *Isr J Med Sci* 15(1): 100; 1979. (no refs)

79-0450 Membrane Fusion as a Mechanism of Simian Virus 40 Entry into Different Cellular Compartments. (Eng) Maul, G. G. (Wistar Inst. Anatomy and Biology, Philadelphia, PA, 19104); Rovera, G.; Vorbrodt, A.; Abramczuk, J. *J Virol* 28(3): 936-944; 1978.

To investigate the possible ways that the simian virus 40 (SV40) particle could pass into the nuclear compartment, permissive (CV1 green monkey kidney) and nonpermissive (mouse embryo) SV40-infected cells were analyzed ultrastructurally. Viral particles were found in the cytoplasm, rough endoplasmic reticulum, nuclear envelope, lysosomes, and mitochondria. Upon entering the cell, the virion obtained a tight membrane envelope. It seemed to be either released from the envelope upon fusion with other membranes of the cell or aggregated into tubular membrane specializations upon fusion with other membrane-enveloped particles. Reconstructed morphological sequences and the finding of SV40 in different spaces of the cell suggest that entry of SV40 into the different compartments and eventually into the replication site was facilitated by its capacity for being enveloped by a variety of membranes (notably, the cell membrane and the nuclear membrane) and the sequential fusion and fission of these membranes. (16 refs)

79-0451 Characterization of the Amino-Terminal Tryptic Peptide of Simian Virus 40 Small-t and

Large-T Antigens. (Eng) Mellor, A. (Translation Lab., Imperial Cancer Res. Fund, London WC2A 3PX, England); Smith, A. E. *J Virol* 28(3): 992-996; 1978.

The amino-terminal tryptic peptide of both forms of simian virus 40 (SV40) tumor antigen (small t and large T) were identified. Small-t and large-T antigen were synthesized in vitro and labeled with methionine donated by initiator transfer RNA. Tryptic peptide fingerprinting was used to identify the amino-terminal peptide of the two proteins. Similar fingerprint analysis of small t and large T made in vitro in the absence of acetyl coenzyme A showed that the mobility of the amino-terminal peptide was changed under these conditions and suggested that the peptide is acetylated. These data establish that the amino-terminal methionine residue of SV40 small t and large T results from an initiation event, not post-translational cleavage, and provides additional evidence that the amino terminus of both proteins is acetylated. The identification of the amino-terminal peptide provides a useful marker for further studies of different forms of T antigen from cells infected with and transformed by SV40 and related viruses. (19 refs)

79-0452 Transcription Pattern of In Vivo-Labeled Late Simian Virus 40 RNA: Equimolar Transcription Beyond the mRNA 3' Terminus. (Eng) Ford, J. P. (Rockefeller Univ., New York, NY, 10021); Hsu, M. T. *J Virol* 28(3): 795-801; 1978.

The pattern of RNA transcription on the late (L) DNA strand late in the simian virus 40 (SV40) infectious cycle was examined by separating pulse-labeled RNA chains according to size and hybridizing them to an ordered series of DNA fragments obtained by restriction enzyme digestion. The data suggested that there is a single major RNA species transcribed from the late DNA strand. The RNA transcript has its 5' end a short distance counterclockwise to map coordinate 0.735 and is synthesized in a clockwise fashion with equimolar transcription for at least 1,000 nucleotides past the 3' terminus of the mRNA at map coordinate 0.175. The largest RNA transcripts are terminated in the region between coordinates 0.43 and 0.655, or 1,300 to 2,400 nucleotides beyond the 3' end of the mRNA at coordinate 0.175. (21 refs)

79-0453 5-Bromodeoxyuridine and Mutagenic Effect of Oncornavirus SV40. (Rus) Varshaver, N. B. (Inst. Molecular Genetics, Moscow, USSR); Gorbunova, L. V.; Lukash, L. L.; Shapiro, N. I. *Dokl Akad Nauk SSSR* 242(3): 707-710; 1978.

To test the hypothesis that the agents that have a synergistic effect with oncornavirus SV40 with respect to cell transformation also show synergism with respect to mutagenesis, the auxotrophic mutant strain of Chinese hamster cells (237-8 glu-ts) was incubated with bromodeoxyuridine (BDU: 10 µg/ml for 48 hr) and were then infected with SV40

(strain 128). To estimate the incidence of reverse mutants, cells were inoculated into minimal medium. The incidence of reverse mutations after combined exposure to SV40 and BDU ranged from 26.1×10^{-6} to 62.7×10^{-6} (in different experiments), compared with $0.54-1.65 \times 10^{-6}$ after exposure to SV40 alone and $13.0-20.9 \times 10^{-6}$ after exposure to BDU alone. (15 refs)

79-0454 Initiation Site for Transcription of Simian Virus 40 DNA at Late Time after Infection (Meeting Abstract). (Eng) Laub, O. (Weizmann Inst. Science, Rehovot, Israel); Bratosin, S.; Horowitz, M.; Aloni, Y. *Isr J Med Sci* 15(1): 98; 1979. (no refs)

79-0455 Electron Microscopic Evidence for Splicing of Simian Virus 40 RNA (Meeting Abstract). (Eng) Bratosin, S. (Weizmann Inst. Science, Rehovot, Israel); Horowitz, M.; Laub, O.; Aloni, Y. *Isr J Med Sci* 15(1): 100; 1979. (no refs)

79-0456 Characterization and Biogenesis of Nuclear Simian Virus 40 RNA (Meeting Abstract). (Eng) Horowitz, M. (Weizmann Inst. Science, Rehovot, Israel); Laub, O.; Bratosin, S.; Reuveni, Y.; Aloni, Y. *Isr J Med Sci* 15(1): 100; 1979. (no refs)

79-0457 Proteins Bound to Heterogeneous Nuclear RNA of Simian-Virus-40-infected Cells. (Eng) Pagoulatos, G. N. (Departement de Biologie Molculaire, Institut Pasteur, 25/28 Rue de Docteur-Roux, F-75724 Paris-Cedex-15, France); Yaniv, M. *Eur J Biochem* 91(1): 1-10; 1978.

The protein patterns in normal and simian virus 40 (SV40)-infected monkey kidney cells were compared. Heterogeneous nuclear RNA-protein (hnRNA-protein) complexes from SV40-infected cells late in infection contained 7%-10% RNA sequences specific to SV40 DNA; these complexes sedimented at 60S-70S. The proteins and RNA of hnRNA followed a parallel pattern in metrizamide gradients and gave a peak with the same mean density of 1.28 g/cm^3 . Two-dimensional gel electrophoresis showed four proteins in the SV40-infected cells that were not present in the normal cells. One of these proteins corresponded to the major capsid protein VP1 of SV40. The other three proteins observed only in the infected cells appeared to be cellular proteins induced by the virus infection. Thus, these proteins are good candidates for specific hnRNA-bound proteins of SV40 nuclear RNA. Actin, which was identified in both normal and infected cells, may have a role in RNA-protein packaging and transport to the cytoplasm. (29 refs)

79-0458 Human Antibodies Reactive with Purified Envelope Antigens of Primate Type C Tumor Viruses. (Eng) Kurth, R. (Friedrich Miescher Lab., Max-Planck-Insts., Spemannstrasse 37-39, 7400 Tubingen, W. Germany); Mikschy, U. *Proc Natl Acad Sci USA* 75(11): 5692-5696; 1978.

Human sera from healthy individuals, previously shown to react with viral antigens in preparations of detergent-disrupted simian C-type viruses, were tested against virus polypeptides purified to homogeneity. Populations of human antibodies reacted with highly purified envelope glycoproteins of the simian sarcoma virus-simian sarcoma-associated virus complex (gp70) and the Friend leukemia virus complex (gp71). Several immunological parameters influencing human antibody binding to C-type tumor virus antigens were characterized. These parameters indicated that human antibodies tend to bind to what is probably a subset of the antigenic determinants on the virus envelope antigens and that different human sera recognize the same antigenic determinants on the virus envelope antigens tested. The possible origin of these antibodies is discussed. (53 refs)

79-0459 Studies on the DNA-Excision Repair in Lymphocytes of Patients with Recurrent Herpes Simplex. (Eng) Fanta, D. (2nd Dept. Dermatology, Ludwig Boltzmann-Institut, Infektiöse venero-dermatologische Erkrankungen, Vienna, Austria); Topaloglou, A.; Altmann, H. *Bull Cancer (Paris)* 65(3): 341-346; 1978.

DNA repair was investigated in lymphocytes from 21 patients with recurrent herpes simplex infections and in 5 healthy controls. The patients (ages 8-82), who were free of other forms of chronic disease, were examined during symptom-free intervals. Semiconservative DNA synthesis was measured by ^3H -thymidine ($10 \mu\text{Ci/ml}$) labeling, the proportion of suppressed DNA synthesis was determined in a hydroxyurea assay, and UV-induced and gamma-radiation-induced DNA repair synthesis was measured by ^3H -thymidine incorporation. The semiconservative DNA synthesis of patients was significantly below control values. Although DNA synthesis activity 30 min after UV exposure was above that of controls, suggesting vigorously progressing repair synthesis, rates were reduced 90 min post-exposure, implying early repair termination. The distributions of DNA synthesis values below those of controls following gamma irradiation showed the persistence of chain breaks caused by this radiation. In four patients studied, the autoradiographic labeling index as well as the av number of grains present were markedly reduced in unscheduled (repair) DNA synthesis. Therefore, herpes simplex interferes with DNA repair mechanisms and increases the risk of late effects in patients with recurrent herpes manifestations. (37 refs)

79-0460 Antibodies to Herpes Simplex Virus Types 1 and 2 in Patients with Squamous-Cell Car-

cinoma of Uterine Cervix in India. (Eng) Seth, P. (Dept. Microbiology, All-India Inst. Medical Sciences, Ansari Nagar, New Delhi-110016, India); Prakash, S. S.; Ghosh, D. *Int J Cancer* 22(6): 708-714; 1978.

The indirect hemagglutination test (IHA) was used to study the occurrence of antibodies to herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in 124 women with squamous cell carcinoma of the uterine cervix, 46 with noncervical cancer, and 116 matched normal controls. Type-specific antibody titers were determined by the IHA inhibition test. A significantly larger proportion of cervical cancer (CC) patients (64.5%) had HSV-2 antibody activity than either the other cancer patients (38%) or controls (36.2%), but there was no difference in the proportions positive for HSV-1 activity. Mean antibody titers to HSV-1 as well as HSV-2 were significantly higher in the CC patients than in the other two groups. However, measurement of type-specific antibodies was of no help in establishing past infection by HSV-2 in CC patients, as no type-specific HSV-2 antibodies were produced in 58%. There were no significant differences in the incidence of HSV-2 antibodies or in HSV-1 or HSV-2 mean antibody titers among the different clinical stages and histological types of CC. The data suggest that HSV-2 may be causally associated with squamous cell CC, but not as a passenger virus of carcinomatous tissue. Further differentiation of this tissue may be a host-controlled mechanism. (26 refs)

79-0461 Quantitative Correlation of Morphological Alterations of the Nucleus with Functional Events During In Vitro Infection of Glial Cells with Herpes Simplex Homini (HSV 2). (Eng) Dupuy-Coin, A. M. (Laboratoire de Pathologie Cellulaire, Institut Biomedical des Cordeliers, 21, Rue de l'Ecole de Medecine, 75270 Paris Cedex 06, France); Arnoult, J.; Bouteille, M. *J Ultrastruct Res* 65(1): 60-72; 1978.

Changes in the ultrastructure of nuclei of cultured human glial cells were examined at various times after viral infection with herpes simplex hominis type 2 (HSV2). Glial cells grown from a biopsy of normal nervous tissue were infected after five passages using HSV2 at a titer of 5×10^5 plaque-forming units/ml. Samples were taken at 3, 5, 6, 8, 14, and 24 hr for electron microscopic examination. The most striking feature of herpes-infected nuclei was the migration of the chromatin toward the nuclear periphery. Nucleolar changes occurred early and soon led to complete nucleolar destruction. At later times, only fibrillar masses surrounding the fibrillar centers could be found. The number of perichromatin granules increased to a considerable extent so that they appeared as closely packed clusters. The number of nuclear bodies decreased with infection time and completely disappeared within 24 hr. Viral nucleocapsids began to appear as early as 8 hr after infection in some cells. These observations combined with previously published data point to the perichromatin granules as the morphological substrates of the viral premessenger RNA. These findings also support the hypothesis that

the protein of nuclear bodies is related to viral proteins. The disappearance of the nuclear bodies as the number of nucleocapsids increases in the nucleus suggests that the protein of the nuclear bodies is used to form the nucleocapsids. (62 refs)

79-0462 Effect of Time and Diet on the Immune Status of Mice Challenged with Herpes-transformed Cells. (Eng) Gridley, D. S. (Loma Linda Univ., Loma Linda, CA, 92354). *Diss Abstr Int* B 39(5): 2139-2140; 1978. (no refs)

79-0463 Long-Term T-Cell-mediated Immunity to Epstein-Barr Virus in Man. I. Complete Regression of Virus-induced Transformation in Cultures of Seropositive Donor Leukocytes. (Eng) Moss, D. J. (Queensland Inst. Medical Res., Bramston Terrace, Brisbane, Queensland 4006, Australia); Rickinson, A. B.; Pope, J. H. *Int J Cancer* 22(6): 662-668; 1978.

A previous observation that adult WBC exposed to potent Epstein-Barr virus (EBV) preparations and cultured at a concentration of 10^6 cells/ml frequently failed to give rise to cell lines if subculture was delayed beyond the first week postinfection was investigated further. Peripheral blood mononuclear cells from donors of known serological status with respect to EBV were exposed to the virus in vitro and then cultured at concentrations of 10^6 or 2.5×10^5 cells/ml. All cultures from nine seronegative adult and 12 fetal donors gave rise to cell lines following subculture 4 wk postinfection. In contrast, seropositive donor cultures seeded at the higher cell concentration developed foci of proliferating EB nuclear antigen-positive cells within the first 1-2 wk but thereafter regressed completely, and subcultures made after 4 wk never gave rise to cell lines. Out of 18 seropositive donors tested, 15 showed regression in all cultures seeded at $\geq 10^6$ cells/ml; with the other three donors, a proportion of replicate cultures regressed. T-cell depletion and reconstitution experiments showed that the effect was absolutely dependent upon the presence in the cultures of T cells from these seropositive donors. The results strongly suggest that the regression phenomenon is an in vitro expression of long-term T-cell-mediated immunity to EBV that most, if not all, infected individuals possess. (25 refs)

79-0464 Seroconversion Against Epstein-Barr Virus in Two Nonhuman Primate Species Infected by the Oropharyngeal Route. (Eng) Glaser, R. (Dept. Medical Microbiology, Ohio State Univ. Sch. Medicine, 333 W. Tenth Ave., Columbus, OH, 43210); Lee, K. J.; Lang, C. M.; Levy, B. *J Infect Dis* 138(5): 695-698; 1978.

The pathogenicity of Epstein-Barr virus (EBV) was investigated in two nonhuman primate species inoculated oro-

pharyngeally. Eight squirrel monkeys were inoculated with EBV by spraying the virus into the nose and throat. Three monkeys were used as mock-infected controls. Serum samples were obtained approx 1 mo apart and analyzed for EBV-specific antibodies (ab's). None of the monkeys seroconverted. The last samples assayed were obtained 113 days after inoculation. The animals were then reinoculated. Sera from all reinfected animals remained negative for at least 104 days after the second inoculation; after that, two monkeys seroconverted, as demonstrated by the presence of ab's to early antigen (EA) and viral capsid antigen (VCA) at 125 days. Both animals lacked ab to EB nuclear antigen (EBNA). By day 166, however, ab to EA disappeared and the titer of ab to VCA decreased. By day 197, both animals were negative. At 197 days, a third monkey had ab to EBNA at a titer of 1:32; no ab to EA or VCA was detected. A possible explanation is given for this unusual ab response. In another experiment, one cotton-ear and two cotton-topped marmosets were inoculated directly into the nasopharyngeal tissue with EBV. One of the cotton-topped marmosets seroconverted 82 days after inoculation, with an ab titer to EA of 1:64 and VCA of 1:256; no ab to EBNA was found. None of the monkeys and marmosets developed disease. (10 refs)

- 79-0465 Somatic Cell Hybrids Between Human Lymphoma Cell Lines. V. IdUrd Inducibility and P3HR-1 Superinfectability of Daudi/HeLa (DAD) and Daudi/P3HR-1 (DIP-1) Cell Lines.** (Eng) Moar, M. H. (Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden); Ber, R.; Klein, G.; Westman, A.; Eriksson, I. *Int J Cancer* 22(6): 669-674; 1978.

Two types of somatic cell hybrids were used in iododeoxyuridine (IdUrd) induction and Epstein-Barr virus (EBV) superinfection studies aimed at further elucidating the regulation of the EBV cycle. The first cell line, DIP-1, a hybrid formed between two human lymphoma EBV producers (Daudi and P3HR-1), contained EBV DNA, expressed the virus-determined nuclear antigen (EBNA), and produced two EBV-associated antigens: early antigen (EA) and viral capsid antigen (VCA). The second cell line, DAD, a hybrid series of clones formed between Daudi and a HeLa cell derivative (D98), differed with regard to the expression of EBNA, EA, VCA, and the content of EBV DNA. EA was regularly induced in the EBV DNA-containing hybrids following IdUrd treatment. This induction was greater in lines spontaneously expressing EA. In two hybrids, DIP-1 and DAD10, VCA and viral DNA synthesis were also induced in the presence of IdUrd, the latter being detected by in situ hybridization with P3HR-1 EBV complementary RNA. DIP-1 was superinfectable by the P3HR-1 EBV strain, whereas the DAD series of hybrids were refractory to P3HR-1 superinfection and lacked EBV receptors. (25 refs)

- 79-0466 Genomic Stability of Gibbon Oncornavirus.** (Eng) Sun, L. (Comparative Oncology Lab.,

Univ. California-Davis, Davis, CA, 95616); Kawakami, T. G.; Matoba, S. I. *J Virol* 28(3): 767-771; 1978.

The 70S RNAs from several gibbon type C viruses were examined for sequence homology by molecular hybridization using complementary DNA probes. All virus isolates shared partial homology in their 70S RNA. However, using any of the complementary DNA (cDNA) probes, the degree of genomic homology varied, indicating that each virus was a distinct substrain. A myelogenous leukemia virus (GaLV-3M) was serially passaged through three unrelated gibbons that sequentially developed the same disease. The genomic homology remained unchanged after the three passages, having greater than 93% homology based on cDNA-70S RNA hybridization and melting temperature analysis of the duplex. The genome from another isolate (SEATO GaLV) was similarly found to be unchanged after the virus was naturally transmitted in gibbons. The genomic variation in the isolates was not therefore, the consequence of recent horizontal transmission from a common virus. It is possible that gibbons in their natural habitat are carriers of SEATO GaLV. (21 refs)

- 79-0467 Antigenic Characterization of a New Gibbon Ape Leukemia Virus Isolate: Seroepidemiologic Assessment of an Outbreak of Gibbon Leukemia.** (Eng) Krakower, J. M. (Lab. Cellular and Molecular Biology, NCI, Bethesda, MD, 20014); Tronick, S. R.; Gallagher, R. E.; Gallo, R. C.; Aaronson, S. A. *Int J Cancer* 22(6): 715-720; 1978.

A C-type virus recently isolated from a leukemic gibbon ape in a colony located on Hall's Island, Bermuda, was characterized with respect to the antigenic properties of its *gag* and *env* gene-coded proteins. This virus, designated GaLV-H, was found to be closely related immunologically to C-type viruses previously isolated from gibbons (GaLV-SF, GaLV-SEATO, GaLV-Br) and from woolly monkeys (simian sarcoma-associated virus). However, GaLV-H was readily differentiated from these isolates in a radioimmunoassay for its *env* gene product, gp70. Seroepidemiology established that GaLV-H was horizontally transmitted among gibbons within the colony. There was no evidence of exposure leading to an immune response to the virus or of viral antigenemia in humans working in association with these animals. (29 refs)

- 79-0468 Virus Detected in Cells Explanted into Tissue Culture from Naturally Occurring Malignant Lymphoma in Rhesus Monkeys.** (Eng) Manning, J. S. (Dept. Bacteriology, Univ. California, Davis, CA, 95616); Griesemer, R. A. *Curr Microbiol* 1(3): 157-162; 1978.

To determine if there might be a common viral etiology to the outbreak of 43 cases of spontaneous lymphoma in one macaque colony within 4 yr, neoplastic lymphoid tissue from 10 rhesus monkeys were explanted into tissue cultures, and the cells were subsequently examined for virus expression by

thin-section electron microscopy. The presence of adenovirus, reovirus, foamy virus, and herpesviruslike (*Herpes simiae*?) nucleoids was revealed. When cell-free filtrates from cultures containing the latter three viruses were added to cultures of normal virus-free rhesus lung cells, a cytopathic effect was produced. Virus particles typical of the explant culture could be demonstrated in infected indicator cells. C-type RNA tumor virus particles were not observed electron microscopically in any of the lymphoma tissues or lymphoma cell cultures examined. It is not known if any of the viruses detected played a role in the etiology of the lymphomas. (31 refs)

- 79-0469 In Vitro RNA-RNA Splicing in Adenovirus 2 mRNA Formation.** (Eng) Blanchard, J. M. (Rockefeller Univ., New York, NY, 10021); Weber, J.; Jelinek, W.; Darnell, J. E. *Proc Natl Acad Sci USA* 75(11): 5344-5348; 1978.

The in vitro conversion of an adenovirus 2 (Ad2) nuclear messenger RNA (mRNA) precursor to a molecule with the size and sequence composition of mature mRNA is described. "Splicing" of the precursor to an Ad mRNA was accomplished in isolated cell-free extracts. Hypotonically swollen HeLa cells were labeled for 10 min with ³H-uridine, and the nuclei were isolated. Addition of "cytoplasmic" extract was required for the reaction to occur. However, because this extract was prepared by swelling cells in hypotonic buffer and stripping the cytoplasm during homogenization, it is likely that some enzyme or cofactor leaked from the nuclei during this preparation. The nuclear precursor, a poly(A)-terminated RNA molecule approx 5 kilo-bases (kb) long, contained sequences complementary to the 58.5-75.9 region of the Ad2 genome, including sequences spliced out of the mature mRNA molecule. The in vitro-spliced product was a poly(A)-terminated RNA molecule identical in size to the cytoplasmic 72,000-mol wt protein mRNA (2 kb long) in which the sequences encoded in the 70.7-75.9 region of the viral genome were spliced to those encoded at 58.7-65.6, with the sequences encoded at 66.1-70.7 deleted. It is concluded that RNA-RNA splicing of parts of a nuclear precursor RNA molecule is probably a general mechanism in mRNA manufacture in higher cells. (39 refs)

- 79-0470 Characterization of a Variant of Human Adenovirus Type 2 Which Multiplies Efficiently in Simian Cells.** (Eng) Klessig, D. F. (Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11524); Hassell, J. A. *J Virol* 28(3): 945-956; 1978.

H2hr400 (abbreviated to hr400), a variant of human adenovirus 2 (Ad2) that grows in simian cells without the help of simian virus 40 (SV40) or simian adenoviruses, was characterized. Genome analysis set an upper limit of 73 base pairs (bp) to the amount of SV40 information that hr400 could

contain. Late viral proteins were synthesized in permissive human cells infected with Ad2, hr400, or Ad2 plus SV40 and in simian cells infected with hr400 or Ad2 plus SV40; these proteins were dramatically reduced in simian cells infected with Ad2 alone. Both the hr400 and the Ad2+ND1 30K protein were able to act in *trans*. The data exclude the possibility that SV40 sequences are present in hr400, allowing it to multiply in simian cells. Using a modified marker rescue technique, the mutation in hr400 was mapped between coordinates 59 and 80 of the viral genome. A point mutation may be responsible for the new phenotype in hr400. (39 refs)

- 79-0471 Genetic Analysis of Adenovirus Type 2. VIII. Physical Locations of Temperature-sensitive Mutations.** (Eng) Hassell, J. A. (Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11524); Weber, J. *J Virol* 28(3): 671-678; 1978.

When 44 wild-type recombinants (*ts*+) viruses obtained in crosses between 4 temperature-sensitive (*ts*) adenovirus type 5 (Ad5) and 4 *ts* Ad2 mutants were analyzed by cleavage with 4 restriction endonucleases (*EcoRI*, *HindIII*, *SmaI*, and *BamHI*), 36 of the recombinants contained both Ad2 and Ad5 sequences. The physical map positions of five Ad2 and Ad5 *ts* mutations were determined: the Ad2 *ts1* mutation mapped near position 59 between positions 57 and 69; Ad2 and *ts3* mapped between 44 and 57 on the physical map; Ad2 *ts4* mapped between 30 and 43; Ad2 *ts48* mapped between 69 and 80; and Ad5 *ts1* mapped between 69 and 71. (37 refs)

- 79-0472 Transcription of the Transforming Region of Adenovirus Type 5 in a Rat Cell Line Transformed by a Small Restriction Fragment.** (Eng) Chinnadurai, G. (Inst. Molecular Virology, St. Louis Univ. Sch. Medicine, St. Louis, MO, 63110); Fujinaga, K.; Rho, M. H.; van der Eb, A. J.; Green, M. *J Virol* 28(3): 1011-1014; 1978.

The fraction of the adenovirus type 5 genome expressed as messenger RNA (mRNA) in a rat cell line, 5RK, transformed by the *HsuI*-G restriction fragment was analyzed by saturation hybridization using separated strands of the ³²P-labeled *HindIII*-G fragment. Between 45% and 50% of the G fragment (about 8 x 10⁵ daltons) was expressed as mRNA. The size of the polyadenylic acid-terminated virus-specific cytoplasmic and nuclear RNA was determined by electrophoresis on polyacrylamide gels containing 98% formamide, followed by hybridization of the gel slices with viral DNA. The major virus-specific RNA species present in the cytoplasm was approx 14S, whereas the major virus-specific RNA present in the nucleus was 30S-32S. The large size of the nuclear virus-specific RNA suggests that the host sequences are covalently linked to the viral transcript. (17 refs)

- 79-0473 Role of DNA Polymerase γ in Adenovirus DNA Replication.** (Eng) van der Vliet, P. C. (Lab. Physiological Chemistry, State Univ. Utrecht, Vondellaan 24 A, 3521 GG Utrecht, Netherlands); Kwant, M. M. *Nature* 276(5687): 532-534; 1978.

The cellular DNA polymerase required for adenovirus (Ad) DNA replication was determined by incubating nuclei from Ad2- or Ad5-infected KB cells with the ingredients necessary for in vitro DNA synthesis and various concentrations of 2',3'-dideoxythymidine triphosphate (ddTTP), which inhibits DNA polymerase γ and β , but not DNA polymerase α or, in similar conditions, cellular DNA or simian virus 40 (SV40) DNA synthesis. Nuclear Ad DNA synthesis was very sensitive to ddTTP, with 50% inhibition occurring at a ddTTP/dTTP ratio of 1.4×10^{-2} . Cellular DNA synthesis was not inhibited up to a ratio of 20. In African Green monkey kidney cells, Ad5 DNA synthesis was very sensitive to ddTTP, but SV40 DNA synthesis was only inhibited when ddTTP was present in at least 20-fold excess compared with dTTP. The inhibition of Ad DNA synthesis was independent of incubation time and could be suppressed by an excess of dTTP. The mechanism of inhibition can be explained by assuming that 2',3'-dideoxythymidine monophosphate is incorporated into growing DNA chains and acts as a chain terminator. DNA polymerases from the KB cells could be distinguished by their different sensitivity to ddTTP: the α form was most resistant (50% inhibition at a ddTTP/dTTP ratio of 30), the β form was partially resistant (50% inhibition at a ratio of 1), and the γ form was most sensitive. It is assumed that DNA polymerase γ is required for chain elongation of Ad replicative intermediates. DNA polymerase γ and mitochondrial DNA polymerase share identical properties, and both Ad DNA and mitochondrial DNA replicate unidirectionally according to a strand-displacement mechanism, in contrast to nuclear DNA synthesis or papovavirus DNA replication. There may be at least two enzymatically distinguishable replication mechanisms in mammalian cells. (19 refs)

- 79-0474 Enhancement of Viral Transformation for Evaluation of the Carcinogenic or Mutagenic Potential of Inorganic Metal Salts.** (Eng) Casto, B. C. (Bio-Labs, Inc., 2910 MacArthur Blvd., Northbrook, IL, 60062); Meyers, J.; DiPaolo, J. A. *Cancer Res* 39(1): 193-198; 1979.

Thirty-eight metal salts were tested for their capacity to enhance the transformation of Syrian hamster embryo cells by a simian adenovirus, SA7. All of the metal salts with known carcinogenic potential in animals or mutagenic activity in microbial or mammalian cells increased the SA7 transformation frequency. Metals were classified into three groups according to the concentration necessary to produce significant enhancement. Those showing highest activity (positive at < 0.05 mM) were the salts of antimony, arsenic, cadmium, chromium, and platinum. The second group (positive from 0.05 to 0.6 mM) included beryllium, cobalt, copper, lead, manganese, mercury, nickel, silver, thallium, and zinc. Iron salts were placed in a third group (only positive at concentrations > 0.9 mM). With the exception of $ZnCl_2$ and $ZnSO_4$, enhancement was demonstrated by both a relative increase in the viral transformation frequency and an absolute increase in the number of transformed foci among treated cells. The latter observation and the demonstration of enhancement in the absence of overt cell killing negate the possibility that enhancement resulted from the selection of transformation-sensitive cells. (54 refs)

- 79-0475 A Cytogenetic Study of the Interactions of Adenovirus and Rat Cells, Infected and Transformed (Meeting Abstract).** (Eng) Gallimore, P. H. (Dept. Cancer Studies, Univ. Birmingham Medical Sch., Birmingham B15 2T3, England). *Heredity (Lond)* 41(part 3): 417; 1978. (no refs)

See also:

- *(Rev.): 79-0065, 79-0066, 79-0067, 79-0068, 79-0069.
- *(Chem.): 79-0212, 79-0216.
- *(Phys.): 79-0375.
- *(Immun.): 79-0479, 79-0482, 79-0487, 79-0490, 79-0493, 79-0494.
- *(Epid.-Biom.): 79-0554, 79-0555, 79-0556.

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- 79-0476 Serological Response to Intracaeal Injections of Antigenic Mouse Tumour Cells.** (Eng) Laursen, M. L. (Fibiger Lab., Ndr. Frihavnsgrde 70, DK-2100 Copenhagen O, Denmark). *Br J Cancer* 38(6): 692-698; 1978

Tumor-specific activity of sera from intracaeally immunized C3H mice was studied by the indirect membrane immunofluorescence technique. These sera apparently contained factors ("interfering factors") able to interfere with the binding of tumor-specific antibodies to antigenic sites on the tumor-cell membrane. These factors were specifically absorbed by the immunizing tumor cells, but they lacked determinants detectable by polyvalent fluorescein isothiocyanate (FITC)-conjugated goat anti-mouse gamma globulin. C3H/L1/a cells treated with a 1:4 dilution of positive-control serum after preincubation with enhancing serum at a dilution of 1:2 showed a higher fluorescent index than cells treated with enhancing serum alone, indicating either that not all antigenic sites were covered by factors in the enhancing serum, or that the interfering factors can be replaced by competing specific antibodies. The interfering phenomenon was only detectable when using serum from animals in which intestinal immunization was followed by enhanced growth of the challenging tumor. No interfering factors were detectable in serum from experiments in which inhibition of tumor growth followed the intestinal immunization. These observations indicate that enhancing serum contains factors with specificity and affinity for tumor-associated antigens, but that compared with the positive-control serum these factors lack certain immunoglobulin determinants. (27 refs)

- 79-0477 Increased Risk of Lymphoma in Sicca Syndrome.** (Eng) Kassan, S. S. (Section Clinical Immunology, Lab. Microbiology and Immunology, Natl. Inst. Dental Res., NIH, Bethesda, MD, 20014); Thomas, T. L.; Moutsopoulos, H. M.; Hoover, R.; Kimberly, R. P.; Budman, D. R.; Costa, J.; Decker, J. L.; Chused, T. M. *Ann Intern Med* 89(6): 888-892; 1978.

The case records of 136 women with sicca syndrome were analyzed to estimate the risk of lymphoma and to search for clinical features associated with its development during the course of the disease. The women were admitted to the National Institutes of Health (NIH) Clinical Center between 1954 and 1975. Seven patients developed non-Hodgkin's lymphoma from 6 mo to 13 yr after their first admission to NIH. This was 43.8 times ($p < 0.01$) the incidence expected from the rates of cancer prevailing among women of the same age range in the general population during this time. In addition, three cases of Waldenstrom's macroglobulinemia occurred in this study group. Eight patients developed cancers other than

lymphoma, similar to the number expected based on the rates prevailing in the general population. Patients with a history of parotid enlargement, splenomegaly, and lymphadenopathy had an increased risk of lymphoma. These clinical conditions did not appear to be early manifestations of undiagnosed lymphoma but rather seemed to identify a subgroup of patients with sicca syndrome with marked lymphoid reactivity, who had a particularly high risk of subsequently developing lymphoma. (36 refs)

- 79-0478 Pre-Morbid Factors in Hodgkin's Disease. II. BCG-Vaccination Status, Tuberculosis, Infectious Diseases, Tonsillectomy, and Appendectomy.** (Eng) Andersen, E. (Medical Dept. C., Gentofte Univ. Hosp., DK-2900 Hellerup, Denmark); Isager, H. *Scand J Haematol* 21(4): 273-277; 1978.

In young adults with Hodgkin's disease (HD), cell mediated immunity (CMI) was evaluated retrospectively from their health records. Sixty-three HD patients were compared with 182 controls matched for sex, age, and socioeconomic background. Information regarding BCG vaccinations, tuberculin skin tests, the frequency of tuberculosis, bacterial and viral diseases, and of tonsillectomy, adenoidectomy, and appendectomy was obtained from the school health records. Two of the Hodgkin's disease patients had had tuberculosis compared with none of the controls. No significant differences were found in the frequency of BCG vaccination, tuberculin reactivity, viral or bacterial diseases, adenoidectomy, tonsillectomy, or appendectomy. Neither complications to nor prolonged course of viral diseases were reported in HD patients or controls. These findings do not support a hypothesis of a pre-morbid CMI deficiency state in HD. They do not, however, exclude a disease-specific defect, which would not be disclosed by this study. (8 refs)

- 79-0479 An Immunodepressant Virus is Not Responsible for the Marked Tumorigenicity of the 13762A Mammary Adenocarcinoma in Syngeneic Fischer Rats (2 Letters to Editor).** (Eng) Huber, S. (Dept. Surgery, Stanford Univ. Medical Center, Stanford, CA, 94305); Lucas, Z. J.; Campbell, D. A.; Herberman, R. B. *Cell Immunol* 41(1): 207-210; 1978.

In view of previous findings (1) that an in vivo-maintained 13762 Fischer mammary adenocarcinoma line was contaminated with Kilham rat virus (KRV) and (2) that the isolated KRV, as well as 13762 tumor cells and cell-free tumor extracts, were cytopathic to lymphocytes and suppressed

in vitro lymphocyte responses to mitogens, allogeneic lymphocytes, and syngeneic tumor cells, the immune response to the 13762 mammary adenocarcinoma (obtained from the same source) was determined in syngeneic Fischer rats. The subline of the 13762A tumor studied was not cytopathic to lymphocytes and did not inhibit other parameters of immunologic activity. Observations on the host response to the tumor indicated that the tumor was immunogenic and was not contaminated with an immunodepressant virus. It appears that the answer to how the tumor circumvents host control in the face of an apparently normal cellular immune response lies in the interrelationships between the autoregulatory features of the immune response and the apparent ready shedding of this tumor's surface antigen. Different results obtained by different laboratories employing the same tumor system may be due to the influence of environment-induced dissimilarities in the tumor sublines. In a reply, it is stated that the above findings do not completely obviate the presence of KRV. (1) The stimulating cells used were not in vivo-passaged cells but were tissue culture-adapted monolayer cells carried within the sterile confines of an incubator. (2) In the first study, evidence for in vitro viral infection usually depended on high levels of cellular turnover, and levels of phytohemagglutinin (PHA) stimulation were higher (25-50,000 cpm) than those presented in the second study (10,000 cpm). (3) In the first study, evidence for viral inhibition depended on longer incubation times (3-5 days vs 2 days) in the PHA assay. A final conclusion should rest on a direct serological assay for the virus in ascites-passaged and tissue culture-adapted cells. (10 refs)

- 79-0480 Heterotransplantation of Human Glioma in Hereditary Asplenic-Athymic Mouse.** (Eng) Yamashita, M. (Neurological Inst., Kyushu Univ., Kyushu, Japan); Takeshita, I.; Kitamura, K. *Gann* 69(5): 735-736; 1978.

A study demonstrating the value of the Lasat mouse, a new strain with asplenia and athymia, in the study of heterotransplantation of human glioma is presented. All mice inoculated with 6×10^6 to 1×10^7 KNS-42 cells developed tumors showing histological and karyotypic features of the original tumor. (3 refs)

- 79-0481 Idiopathic Cardiomyopathy, Age, and Suppressor-Cell Dysfunction as Risk Determinants of Lymphoma after Cardiac Transplantation.** (Eng) Anderson, J. L. (Cardiology Div., Univ. Michigan Sch. Medicine, Ann Arbor, MI, 48109); Fowles, R. E.; Bieber, C. P.; Stinson, E. B. *Lancet* 2(8101): 1174-1177; 1978.

A review of lymphomas developing in recipients of cardiac allografts has yielded significant risk factors. Frequency varied strikingly according to original cardiac disease: lymphoma developed in 6/37 patients with prior idiopathic car-

diomyopathy (ICM) but in none of 54 patients with prior coronary-artery disease (CAD). All patients who developed lymphomas were aged under 40. Combination of both risk factors (ICM and age < 40) produced a subgroup with a highly significantly increased risk of lymphoma. ICM, but not CAD, was characterized by a defect in mitogen-induced mononuclear cell suppressor activity. It is postulated that defective regulation in the immune systems of younger patients under chronic alloantigen stimulation may allow lymphoid proliferation to proceed to lymphoreticular malignancy. Immunosuppressive agents such as azathioprine may exert a co-oncogenic effect. (19 refs)

- 79-0482 Primary Neoplastic Transformation In Vivo of Xenogeneic Skin Grafts on Nude Mice.** (Eng) Kreider, J. W. (Dept. Pathology, Specialized Cancer Res. Center, Coll. Medicine, Pennsylvania State Univ., Hershey, PA, 17033); Bartlett, G. L.; Sharkey, F. E. *Cancer Res* 39(1): 272-276; 1979.

The skin of New Zealand White rabbits was infected with Shope papilloma virus and grafted orthotopically to noninbred Swiss nude mice. Typical Shope rabbit papillomas developed in 11/12 grafts, but 8 similarly treated nude mouse skin grafts were not altered. These results demonstrate that the xenogeneic tissues retained their susceptibility to oncogenic agents after transplantation to nude mice. It should be feasible to study the carcinogenesis of human tissues in this system. (13 refs)

- 79-0483 Plasmacytoma Spleen Colonization: A Sensitive, Quantitative In Vivo Assay for Idiotypic-Specific Immune Suppression of MOPC-315.** (Eng) Daley, M. J. (Dept. Pathology, Immunobiology Labs., Univ. New Mexico Sch. Medicine, Albuquerque, NM, 87131); Bridges, S. H.; Lynch, R. G. *J Immunol Methods* 24(1/2): 47-56; 1978.

A spleen colony-forming assay that can detect the tumor-specific transplantation immunity directed to idiotype antigens in the surface membrane of MOPC-315 myeloma cells was developed. The assay measures those clonogenic cells of the myeloma that have a sufficient proliferative capacity to form macroscopic splenic foci within 14 days after iv challenge. BALB/c mice were inoculated iv with $4-8 \times 10^4$ viable spleen-passaged MOPC-315 (MOPC-315-s) cells prepared from myelomatous spleens. Fourteen days later, mice were anesthetized and sacrificed by cervical dislocation, and their spleens were removed and placed in vials containing Bouin's fixative. After 24 hr, the spleens were examined, and all visible and distinct nodules were counted. In normal BALB/c mice, there was a linear relationship between the number of MOPC-315 cells injected and the number of plasmacytoma colony-forming units (PCFU, spleen) observed within the range of 1-90 PCFU's per spleen. Idiotype-specific

myeloma graft resistance induced by immunization with the specifically purified dinitrophenol-binding IgA paraprotein of MOPC-315 could also be measured. The assay is highly quantitative, sensitive, reproducible, less time-consuming, and superior to conventional in vivo assays. The magnitude of resistance was apparently increased when systemic rather than local (sc) challenge was performed. One implication of a vigorous systemic idiotypic-specific resistance relates to the disseminated state that characterizes human idiotypic-bearing B-cell neoplasms such as myeloma and chronic lymphocytic leukemia when they are initially detected. (27 refs)

79-0484 Regulation of the Immune Response to Tumor Antigen. IV. Tumor Antigen-specific Suppressor Factor(s) Bear I-J Determinants and Induce Suppressor T Cells In Vivo. (Eng) Perry, L. L. (Dept. Pathology, Harvard Medical Sch., 25 Shattuck St., Boston, MA, 02115); Benacerraf, B.; Greene, M. I. *J Immunol* 121(6): 2144-2147; 1978.

The fine immunochemical specificity of the tumor-induced suppressor factor(s) and the mechanism by which it may operate in vivo were analyzed further. The suppressor factor(s) specific for the S1509a methylcholanthrene-induced fibrosarcoma was shown to bear determinants encoded by the I-J subregion of the murine major histocompatibility complex, since suppressive activity was removed by passage of the factor through an immunoadsorbent composed of anti-I-Jk coupled to Sepharose. No loss of activity was observed after passage of the factor through control columns composed of normal mouse globulin. Furthermore, activity could be recovered from the relevant immunoadsorbent by elution with high salt. The administration of crude suppressor factor(s) to normal animals for 4 days resulted in the development of a population of suppressor cells that acted in a manner analogous to the suppressor cell population used to produce the factor. These factor-induced suppressor cells were T cells, and they exhibited an antigen specificity similar to that displayed by the tumor-induced suppressor cells. Thus, the tumor-specific suppressor factor(s) bears I-J determinants and is capable of inducing the appearance of suppressor T cells in the non-tumor-bearing host. These cells may then act in a specific manner to limit host responsiveness to tumor antigen. (21 refs)

79-0485 Characteristic of Tumor-Associated Antigen in Chemically Induced Urinary Bladder Cancer of Rats. (Eng) Hashimoto, Y. (Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama, Aramaki, Sendai 980, Japan). In: *Gann Mongr Cancer Res* (21): 3-10; 1978.

The antigenic characteristics of seven bladder cancers induced in inbred ACI/N rats by N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN) were studied by different immunological methods. A common antigen was detected in three cancer

lines by an immunofluorescence test using anti-BC47 serum that was induced in allogeneic rats and absorbed with normal ACI rat cells. This common antigen was not related to tumor-specific transplantation antigen, which suggests that it is a tumor-associated antigen, although it may not act as an immunogen in the histocompatible host. By transplantation immunity in syngeneic rats, 2/6 cancer lines showed a high antigenicity, whereas the other four lines had low or undetectable antigenicity. The two highly antigenic cancers gave rise to cross resistance in immunized rats. However, this may not have been due to the existence of a common antigen in the cancers, since lymphoid cells from rats immunized with one cancer did not kill cancer cells of the other lines. (22 refs)

79-0486 Tumor-associated Antigens of Rat Moloney Sarcoma Cells. I. Cell-Surface Antigens. (Eng) Leung, K. (Dept. Immunopathology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037); Jones, J. M.; Feldman, J. D. *J Immunol* 121(5): 1836-1843; 1978.

The dissociated cell surface membranes of a rat Moloney sarcoma (MST), derived from a BN rat, were extracted with 2 M KI, with 6 M guanidine thiocyanate, or by papain digestion. Extracts obtained with these three reagents were fractionated on columns of controlled-pore glass (170 Å pore size). A fraction was eluted from each preparation that contained tumor-associated antigens (TAA), viral, fetal, and histocompatibility antigens. With an antibody specific for TAA, the TAA, devoid of detectable viral, fetal, and histocompatibility antigens, were coprecipitated by addition of goat antibody to rat immunoglobulin. After electrophoresis on slab gels, three bands were detected with estimated mol wts of 185,000, 150,000, and 70,000. These bands were not detected on slab gel electrophoresis with extracts of BC5, a chemically induced tumor (BC5), normal BN lymphoid cells, M-MuLV, or Moloney murine leukemia virus fetuses, after incubation with anti-TAA antibody and goat antibody to rat immunoglobulin. TAA extracts prepared with 2 M KI, 6 M guanidine thiocyanate, or papain digestion showed immunologic reactivity. Cold TAA inhibited the coprecipitation of labeled TAA by rat antibody specific for TAA; they elicited antibody in guinea pigs but not in rats; and antibodies specific for TAA were cytotoxic to MST in the presence of complement. (48 refs)

79-0487 Tumor-associated Antigens of Rat Moloney Sarcoma Cells. II. Cytosol Antigens. (Eng) Leung, K. (Dept. Immunopathology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037); Feldman, J. D. *J Immunol* 121(5): 1844-1848; 1978.

BN rat Moloney sarcoma cells (MST) were pulsed with ³⁵S-L-methionine for 10 and 60 min and lysed by vortexing in 0.5% deoxycholate, 0.5% NP₄₀, 0.02 M Tris, 0.04 M

NaCl, pH 7.5, for 30 sec. The lysate was centrifuged at 16,300 x g for 10 min, and the supernatant was coprecipitated with immunoglobulin fractions of normal BN serum, normal Lewis serum, BN antiserum to Moloney sarcoma cells (BNaMST), BN antiserum to tumor-associated antigens (BNaTAA), BN antiserum to murine leukemia virus (BNa-MuLV), BN antiserum to p30 (BNap30), BN antiserum to gp70 (BNagp70), Lewis antiserum to BN (LeaBN), and BN antiserum to BC5 tumor (BNaBC5). With BNaTAA and BNaMST, a cytoplasmic TAA with a mol wt of 85,000 was detected. In addition, BNaTAA detected three other species of cytoplasmic TAA with mol wts of 220,000, 170,000, and 39,000. The BNaTAA-precipitated entities were unique to MST cells and unrelated to viral, fetal, or histocompatibility antigens. (13 refs)

79-0488 Exogenous Immunoglobulin and the Macrophage Origin of Reed-Sternberg Cells in Hodgkin's Disease. (Eng) Kadin, M. E. (Dept. Lab. Medicine, SB-10, Univ. Washington, Seattle, WA, 98195); Stites, D. P.; Levy, R.; Warnke, R. *N Engl J Med* 299(22): 1208-1214; 1978.

To clarify the nature of Hodgkin cells and their immunoglobulin (Ig), the surface-membrane and cytoplasmic Ig of freshly isolated, viable Reed-Sternberg (R-S) cells from 14 Hodgkin's disease patients was examined with highly specific F(ab'), antisera, which consistently give monoclonal staining in non-Hodgkin lymphomas. Individual R-S cells were examined simultaneously for κ and λ light chains with the use of mixed F(ab'), fragments of antibodies labeled with fluorescein and rhodamine isothiocyanate. It was found that the Ig in R-S cells is predominantly IgG (in one case, IgM was also present) and is always polyclonal. It is probably derived from Ig bound to the membrane of R-S cells in vivo, possibly as the antibody portion of immune complexes circulating in the serum of Hodgkin's disease patients. The capacity of R-S cells to bind and internalize exogenous aggregates of IgG and immune complexes of sheep RBC with IgG or IgM and complement was confirmed in vitro; thus, R-S cells are similar to normal peripheral blood monocytes. The nonrandom uptake of Ig by R-S cells in vivo was inferred from the apparent absence of other common plasma proteins, albumin and fibrinogen, in freshly isolated R-S cells and exclusion by the cells of trypan blue dye. The uptake is probably mediated by the Fc receptor or antigen(s) associated with Hodgkin's disease at the cell membrane. The results favor a macrophage origin for the R-S cell. (29 refs)

79-0489 Effects on In Vitro Tumor Growth of Murine Macrophages Isolated from Sarcoma Lines Differing in Immunogenicity and Metastasizing Capacity. (Eng) Mantovani, A. (Istituto di Ricerche Farmacologiche "Mario Negri", Via Eritrea, 62--20157 Milan, Italy). *Int J Cancer* 22(6): 741-746; 1978.

The effects on in vitro tumor growth of murine macrophages isolated from a chemically-induced, strongly immunogenic, non-metastasizing FS6 sarcoma and from a weakly immunogenic, metastasizing line (mFS6) of the same tumor were investigated. Macrophages isolated from the FS6 sarcoma non-specifically inhibited growth and DNA synthesis of tumor cells in vitro. After culture, FS6 macrophages rapidly lost their cytotoxic activity and became capable of nonspecifically stimulating tumor growth in vitro. Macrophages obtained from the mFS6 tumor nonspecifically enhanced the proliferative activity of tumor target cells and this capacity was maintained when the macrophages were cultured. The results are in keeping with the hypothesis that mononuclear phagocytes may play a role in the regulation of tumor growth and metastasis. (28 refs)

79-0490 In Vitro Sensitization of Lymphocytes Against Murine Viral Associated Antigens by Antigen-fed Macrophages. (Eng) Treves, A. J. (Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305); Honsik, C.; Lieberman, M.; Decleve, A.; Feldman, M.; Kaplan, H. S. In: *The Macrophage and Cancer. Proceedings of the European Reticuloendothelial Society Symposium held in Edinburgh, September 12-14, 1977.* European Reticuloendothelial Society (Edinburgh, Scotland): 448 pp.; 108-117; 1977.

Cell-mediated immunity against both viral particles and various viral antigens was induced in vitro by antigen-fed macrophages. Peritoneal radiation leukemia virus (RadLV)-fed macrophages obtained from (C57BL/Ka x BALB/c)F₁ mice sensitized spleen cells (SC) in vitro so that they became cytotoxic to the virus-infected target cells, BL-6(RadLV). Cell-free extracts from infected and noninfected (BL-5) fibroblast lines and noninfected intact BL-5 lines were also susceptible. Cell-free extracts from three nonproducer lymphoma cell lines (VL₁, RL-12, and R₀) were also immunogenic, but extracts from normal thymocytes and intact mouse embryo fibroblasts were much less so. Cellular components were not necessary for the sensitization, but direct incubation of viruses with SC did not result in immunogenic activity. SC sensitized with first-passage mouse embryo fibroblast-fed macrophages infected with BL/Ka(6) virus and then tested for cytotoxicity only showed activity against fibroblasts infected with the same virus. The effector capacity of macrophage-sensitized lymphocytes could be measured by an end-labeling assay of remaining target cells but not by a pre-labeling assay, as could directly sensitized lymphocytes. In vivo, RadLV-fed macrophages had no influence on tumor growth when injected simultaneously with VL₁ lymphoma cells, but they markedly inhibited tumor development and increased survival when injected 4 days before tumor cells. It is suggested that different subpopulations of T lymphocytes are induced by the sensitization procedures. (21 refs)

79-0491 A T-dependent Factor in Mouse Serum Suppressing Lymphocytic Anti-tumour Cytotoxicity

ty. (Eng) Rao, P. E. (Cornell Univ. Medical Coll., 1300 York Ave., New York, NY, 10021); Sussdorf, D. H. *Immunology* 35(6): 907-915; 1978.

The observation that sera of BALB/c mice bearing urethane-induced lung adenomas contained a factor capable of inhibiting the cytotoxicity of lymphocytes sensitized to the tumor is reported, and the results of experiments in which the factor was sought in the sera of non-tumor-bearing animals are presented. Sera from athymic mice, both normal and tumor bearing, were also examined, as well as sera from thymus-implanted nude mice. The cellular target of the factor was determined by absorption experiments using tumor cells, normal lymphocytes, or tumor-sensitized lymphocytes. The mol wt of the suppressive factor was estimated using Sephadex gel filtration and sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). The suppressive factor was stable to heating at 56 C for 30 min and was unaffected by freezing and thawing. Pretreatment of tumor targets with serum before the addition of lymphocytes was not protective, but pretreatment of sensitized lymphocytes with serum inhibited their cytotoxicity to the same extent as did treatment of the whole culture with serum. Suppressive activity could be removed from serum by absorption with sensitized, but not with unsensitized lymphocytes. While sera from syngeneic or adenoma-bearing nude mice were free of suppressive activity, the activity appeared in nude mice following thymus implantation. When whole BALB/c serum was fractionated on a Sephadex G-200 Column, suppressive activity equivalent to that found in the whole serum was observed consistently in protein fractions eluting in the region of 14,000 daltons. No activity was found in this region when sera lacking suppressive ability were separated. Electrophoresis of fractions representing the activity zone revealed a protein with a mol wt of 14,000 daltons that was present in fractions from active sera, but absent from fractions of inactive sera. Electrophoresis of fractions without suppressive activity did not produce this band. Both the activity zone in the Sephadex profile and the SDS-PAGE band could be demonstrated with sera from thymus-restored nude mice. The observations indicate the existence of a low-mol wt protein in the circulation of normal BALB/c mice that is capable of in vitro suppression of cell-mediated anti-tumor cytotoxicity. The presence of this factor appears to be thymus-dependent, and it seems to exert its effect by binding to sensitized killer lymphocytes. (24 refs)

79-0492 K Chain Variable Regions from Three Galactan Binding Myeloma Proteins. (Eng) Rao, D. N. (Lab. Cell Biology, NCI, NIH, Bethesda, MD, 20014); Rudikoff, S.; Potter, M. *Biochemistry* 17(25): 5555-5559; 1978.

Structural studies of the kappa light chains of the BALB/c mouse myeloma proteins X-24, X-44, and T-601, all of which display binding specificity for antigens containing $\beta(1 \rightarrow 6)$ -D-galactopyranosyl moieties, were carried out. Amino

acid (AA) sequencing and fragmentation by CNBr were used for the structural analysis. A high degree of homology was observed in the first 108 AA of the amino termini of the three proteins. X-24 and T-601 were identical over the first 99 AA and differed only at positions 100 and 106. X-44 differed from the others at position 96 in the third light chain complementarity determining region, but was identical to X-24 at position 106. The presence of a different AA in each protein at position 100 suggests the possibility of multiple genes existing for this segment of the molecule. The change of X-44 at position 96 of tryptophan for isoleucine is interesting, as it involves a change in all three codon bases. X-24 and T-601 are the first pair of light chains to exhibit perfect identity over their variable regions, and the minimal variation seen in all these anti-galactan light chains favors the hypothesis that at least one germ line is required to code for these structures. (37 refs)

79-0493 Self-Nonself Concept for Cancer and Diseases Previously Known as "Autoimmune" Diseases. (Eng) Levine, P. (Ortho Res. Foundation, Raritan, NJ, 08869). *Proc Natl Acad Sci USA* 75(11): 5697-5701; 1978.

The illegitimate glycosphingolipid antigens of the P blood group system and of the Forssman (Fs) tissue antigen in adenocarcinoma, which are foreign to the host, suggest the self-nonself concept, which applies also to diseases such as rheumatoid arthritis, lupus, glomerulonephritis, and idiopathic acute hemolytic anemia. In the presence of glycosphingolipid antigens such as ABO, P, and Fs, the normal serum of the homozygote recessive precursor contains antibodies for the missing antigen(s). The expected antibody to the Fs antigen was present in about 75% of normal men and women. In cancer sera, the incidence of anti-Fs was decreased to about 35%-40%. Anti-Fs was present in 90% of normal sera in the youngest group; this value gradually diminished in the other groups, and the incidence of the antibody in the 70-yr age group was about 60%. The rate of loss of anti-Fs with increasing years appears to parallel the gradual loss of anti-A and anti-B isoagglutinin titers. This phenomenon may be associated with the gradual diminution of protein synthesis with aging or the continuous accumulation of soluble immune complexes in the serum, or both. The self-nonself concept may also be the basis for the pathogenesis of rheumatoid arthritis, lupus erythematosus, idiopathic acute hemolytic anemia, and numerous other conditions classified as "autoimmune" diseases. Some of these diseases are induced by viruses or drugs or both. When a virus or drug attaches itself to the membrane of a tissue cell, the self is converted to nonself which, in rheumatoid arthritis, alters its self immunoglobulin (Ig) to nonself Ig. (31 refs)

79-0494 Activation of Latent Epstein-Barr Virus by Antibody to Human IgM. (Eng) Tovey, M. G. (Lab. Viral Oncology, Institut de Recherches Scientifiques

sur le Cancer, Villejuif, France); Lenoir, G.; Begon-Lours, J. *Nature* 276(5685): 270-272; 1978.

The activation of latent Epstein-Barr virus (EBV) by treatment of human lymphoid cell lines with antisera to human IgM is reported. Treatment of Burkitt's lymphoma-derived Raji cells with antiserum directed against human immunoglobulins increased the number of cells expressing the EBV-specific early antigen (EA) by up to 5,000-fold. Induction of EBV EA was greater with antiserum than with 5-iodo-2-deoxyuridine (IUdR) or 12-O-tetradecanoylphorbol-13-acetate and was greater with antiserum and IUdR combined than with either agent alone. The activity of the anti-human IgM serum was specific for human IgM, and its effect was due to its anti- μ -chain activity. EA induction by anti- μ antibody cannot be explained simply as a nonspecific mitogenic effect. The block in the abortive cycle of Raji cells appeared to be after EA and DNA polymerase synthesis and was independent of the level of induction. Variations in the responses of other cell lines to the anti-IgM antibody were observed, and they may have been due to differences in the amount and/or expression of surface-bound IgM. Activation of the latent EBV genome by antiserum to human IgM may result either from a direct stimulation of virus replication by the antiserum or from combination of the antiserum with surface-bound immunoglobulin. (33 refs)

desired specificity. Sp2/0-Ag14 was resistant to 8-azaguanine, died in HAT-supplemented medium, and had about 73 chromosomes. It was fused with spleen cells from mice immunized with trinitrophenyl (TNP)-derivatized keyhole limpet hemocyanin (TNP-KLH) to yield eight growing cultures. IgM, which did not have TNP specificity, was secreted by four of the cultures, and IgG, which did show TNP specificity, was secreted by the other four. The clones could be distinguished by the mobility of the light or heavy chain. Revertant hybridomas expressing the sheep RBC-specific IgG2b of the progenitor cell line constituted less than one in 5×10^4 of the TNP-specific hybridoma cells. As shown by their karyotypes, the TNP-specific cell lines were hybrids of Sp2/0-Ag14 and mouse cells. Ip injection of TNP-specific hybridoma cells into BALB/c mice caused tumors and yielded ascites fluid with high titers of the TNP-specific Ig. (12 refs)

See also:

*(Rev.): 79-0070, 79-0072, 79-0093.

*(Chem.): 79-0100, 79-0129, 79-0204, 79-0235, 79-0268, 79-0274.

*(Phys.): 79-0358, 79-0387.

*(Viral): 79-0410, 79-0411, 79-0416, 79-0418, 79-0419, 79-0423, 79-0430, 79-0431, 79-0434, 79-0435, 79-0435, 79-0436, 79-0438, 79-0442, 79-0458, 79-0460, 79-0462, 79-0463, 79-0464.

*(Path.): 79-0530.

*(Epid.-Biom.): 79-0560.

79-0495 A Better Cell Line for Making Hybridomas Secreting Specific Antibodies. (Eng) Schulman, M. (Basel Inst. Immunology, Grenzacherstrasse 487, Postfach, 4005 Basel 5, Switzerland); Wilde, C. D.; Kohler, G. *Nature* 276(5685): 269-270; 1978.

A mouse myeloma cell line (Sp2/0-Ag14) was isolated that made no immunoglobulin (Ig) but could be fused with spleen cells to yield hybrids (hybridomas) secreting antibody of

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- 79-0496 Malignant Lymphoma in Four of Five Siblings.** (Eng) Nagel, G. A. (Departement fur Innere Medizin, Kantonsspital Basle, Basle, Switzerland); Nagel-Studer, E.; Seiler, W.; Hofer, H. O. *Int J Cancer* 22(6): 675-678; 1978.

A family in which four of five sisters developed malignant lymphoma and two other relatives had Hodgkin's disease (HD) is reported. Two sisters had the nodular sclerosis type of HD, the third had the lymphocyte-depleted type, and the fourth had a diffuse small-cell reticulum sarcoma affecting the entire lymph-node system, spleen, tonsils, lungs, liver, kidneys, meninges, brain, peripheral nerves, and bone marrow. The first and last patients died of their diseases, while the disease in the other two sisters had remained in remission following radiotherapy. The histocompatibility antigen (HLA)-haplotypes were identical in the three patients studied, while that of the one healthy sibling differed. An uncle of the five sisters (one of their father's 16 siblings) and a second-degree cousin (son of the father's cousin) had both died with HD. It is possible that a genetically determined susceptibility to malignant lymphoma occurred in this family. (26 refs)

- 79-0497 Lymphoma after S.L.E. (Letter to Editor).** (Eng) Barrett, A. (Inst. Cancer Res., Sutton, Surrey SM2 5PT, England); Fitzharris, B. M.; Robson, T.; Smyth, J. F. *Lancet* 2(8099): 1102; 1978.

Two cases of non-Hodgkin lymphoma, one associated with systemic lupus erythematosus (SLE) and one with rheumatoid arthritis, are presented. The lymphomas developed many years after the onset of autoimmune disease, and immunodeficiency may have been a causative factor. Neither patient had received immunosuppressive drugs other than steroids. (no refs)

- 79-0498 Preleukemic Syndromes.** (Eng) Pierre, R. V. (Mayo Clinic, 200 First St. S.W., Rochester, MN). *Virchows Arch Cell Pathol* 29(1/2): 29-37; 1978.

To determine whether cytogenetic studies would be helpful in the diagnosis of preleukemic phases of acute nonlymphocytic leukemia (ANLL), and secondarily to study the prognostic significance of any observed cytogenetic abnormality, a prospective study was carried out on 284 patients with suspected preleukemia. Of these, 62 patients were identified with progression to overt ANLL. Of suspected preleukemic patients, 30% had cytogenetic abnormalities whereas

53% of patients progressing to ANLL exhibited cytogenetic abnormalities. From this data it is suggested that the presence of cytogenetic abnormalities aid in the recognition of preleukemia but are not specific for early leukemia. Furthermore, it is concluded that patients with defective chromosomes (as determined from banding studies) are more likely to develop overt ANLL. (16 refs)

- 79-0499 Complex Chromosome Rearrangements in Chronic Myelocytic Leukemia (Meeting Abstract).** (Eng) Pasquali, F. (Istituto Biologia Generale e Genetica Medica, Univ. Pavia, Pavia, Italy); Francesconi, D. *Clin Genet* 14(5): 306-307; 1978. (no refs)

- 79-0500 Non-Random Clonal Evolution in 46 Cases of Chronic Myeloid Leukemia (Meeting Abstract).** (Eng) Stoll, C. (Clinique Infantile, CHU, Strasbourg, France); Oberling, F. *Clin Genet* 14(5): 312-313; 1978. (no refs)

- 79-0501 Erythrocyte Abnormalities Induced by Chemotherapy and Radiotherapy: Induction of Preleukaemic States?** (Eng) Renoux, M. (Service d'Hematologie Clinique, Hopital Beaujon, 100 boulevard du General Leclerc, 92118 Clichy Cedex, France); Bernard, J. F.; Torres, M.; Schlegel, N.; Amar, M.; Lopez, M.; Boivin, P. *Scand J Haematol* 21(4): 323-332; 1978.

Parameters frequently affected in leukemia, preleukemic states, and bone marrow insufficiency were studied in 21 patients with multiple myeloma (MM) and 33 patients with nonhematologic malignancies before and after chemotherapy. Fourteen of the cancer patients had received prior radiotherapy. Before chemotherapy, the only abnormality was found in the MM patients was an elevated HbF level in one patient. After chemotherapy, MM patients had the following RBC abnormalities: pyruvate kinase (PK) deficiency (58% of patients), increased HbF level (47%), abnormal bone marrow sideroblasts (30%), and modification of blood group antigens (BGA: 68%). No phosphofructokinase (PFK) deficiency was found. In the patients with nonhematologic malignancies, prechemotherapy abnormalities were found only in patients that had received prior radiotherapy, and they consisted of a slight decrease in PK activity (2 patients), decreased PFK activity (1), and modification of BGA (2). After chemotherapy, the patients with nonhematologic malignancies had the following abnormalities: PK deficiency (50%), PFK deficiency (20%), increased HbF level (10%), and modification of BGA (40%). In both patient groups, the

abnormalities, which are usually associated with dysmyelopoiesis and preleukemic states, generally appeared after three monthly courses of chemotherapy, and they appeared more frequently and with greater intensity after combined chemo- and radiotherapy. It is cautioned that none of these parameters are specific to malignant states. (41 refs)

- 79-0502 Abnormalities of Chromosome No. 1: Significance in Malignant Transformation.** (Eng) Rowley, J. D. (Dept. Medicine, Univ. Chicago, Chicago, IL, 60637). *Virchows Arch Cell Pathol* 29(1/2): 139-144; 1978.

To identify the nonrandom abnormalities of whole chromosomes as well as the specific region of chromosome involved, human hematologic malignancies were investigated. Results of banding studies disclosed that in myeloid cells from each of 35 patients with various disorders including acute leukemia, polycythemia vera, and myelofibrosis, clonal alterations leading to either an excess of chromosome number 1, or a partial excess of number 1, was accompanied by trisomy for bands 1q25 to 1q32. Analogous cytogenetic aberrations were consistently noted in solid tumors as well. Evidence showing that the break points in reciprocal translocations that involve chromosome Number 1 occurred almost exclusively in the short arm suggests that this arrangement was not the result of a particularly fragile site between these particular bands. It is now possible to correlate the nonrandom cytogenetic aberrations with specific gene loci. Further study may reveal the gene sequences related to malignancy. (23 refs)

- 79-0503 Cytogenetics of Acute and Chronic Myelofibrosis.** (Eng) Nowell, P. C. (Dept. Pathology, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104); Finan, J. B. *Virchows Arch Cell Pathol* 29(1/2): 45-50; 1978.

A review is presented of the relationship between studies of chromosome structure and the development of acute and chronic myelofibrosis. In both acute and chronic myelofibrosis, in addition to other lymphoproliferative disorders that initiate an increased risk for progression to leukemia, a clone of hemic cells with a chromosome defect is fairly common. Unfortunately, the presence or absence of a cytogenetic alteration has yet to show prognostic value with respect to subsequent clinical course. Chromosome studies indicate that no one particular karyotypic transformation can be associated with myelofibrosis specifically, as many of the same non-random alterations are found in other leukemic and preleukemic conditions. Additionally, both cytogenetic and isoenzyme data suggest that the fibrous tissue in the bone marrow is not related to the myeloproliferative clone. (9 refs)

- 79-0504 A Family with Acute Leukemia, Hypoplastic Anemia and Cerebellar Ataxia. Association with**

Bone Marrow C-Monosomy. (Eng) Li, F. P. (Sidney Farber Cancer Inst., 35 Binney St., Boston, MA, 02115); Potter, N. U.; Buchanan, G. R.; Vawter, G.; Whang-peng, J.; Rosen, R. B. *Am J Med* 65(6): 933-940; 1978.

A family case-study is presented in which the proband, a 6-yr-old boy, is the brother of three other boys who died with hematologic malignancies: the eldest brother died of acute myelogenous leukemia at 10 yr of age, and the second and third eldest brothers died of hypoplastic anemia at ages 5 and 9 yr, respectively. The surviving brother manifests abnormalities that suggest a preleukemic state such as mild pancytopenia, platelet dysfunction, and immunodeficiency. His 17-yr-old sister has a mild normochromic normocytic anemia. Cytogenetic banding studies revealed C-group monosomy in the bone marrows of the proband and third brother, and also that chromosome Number 8 was missing in the proband. At least four of the children and the father had cerebellar ataxia and evidence of a small cerebellum at autopsy or when examined by computerized axial tomography. It is concluded that the array of aberrations exhibited by this family may constitute a new genetic syndrome. (42 refs)

- 79-0505 A 14q+ Chromosome in a B-Cell ALL and a Case of Leukaemic Non-Endemic Burkitt's Lymphoma (Meeting Abstract).** (Eng) Slater, R. M. (Lab. Human Genetics, Univ. Amsterdam, Amsterdam, Netherlands); Philip, P.; Badsberg, E.; Behrendt, H.; Hansen, N. E.; van Heerde, P. *Clin Genet* 14(5): 311-312; 1978. (no refs)

- 79-0506 Chromosomal Abnormalities and Malignant Diseases (Meeting Abstract).** (Eng) Ballesta, F. (Dept. Pediatrics, Genetics Centre, Hospital Clinico y Provincial, Barcelona, Spain); Cruz, M. *Clin Genet* 14(5): 277-279; 1978. (15 refs)

- 79-0507 Frequencies of Sister Chromatid Exchanges in Bloom's Syndrome Fibroblasts (Meeting Abstract).** (Eng) van Bull, P. P. (Dept. Radiation Genetics and Chemical Mutagenesis, Univ. Leiden, Sylvius Lab., Leiden, Netherlands); Vergegaal, P. A.; Natarajan, A. T. *Clin Genet* 14(5): 283; 1978. (no refs)

- 79-0508 Dermatoglyphic Studies in Malignant Melanoma (Meeting Abstract).** (Eng) Tsambaos, D. (Dept. Dermatology, Univ. Duesseldorf, Duesseldorf, W. Germany); Strassburger, D. *Clin Genet* 14(5): 314; 1978. (no refs)

- 79-0509 Carotid Body Tumours. A Report of Twelve Cases.** (Eng) Bergdahl, L. (Thoracic Surgery Clinic, Karolinska Sjukhuset, Stockholm, Sweden). *Scand J Thorac Cardiovasc Surg* 12(3): 275-279; 1978.

Twelve case reports of carotid body tumors established by histological examination were collected from various hospitals throughout Sweden and are summarized. One patient was diagnosed to have such a malignant tumor 24 yr after receiving radiation treatment for a benign tumor on the same side of the neck. Although there is well documented evidence of thyroid carcinomas developing after such irradiation for benign neck disorders, the development of carotid body tumors has not been reported. Definitive diagnosis was obtained in 6 patients by carotid angiography, and in 1 patient (of 10 investigated) by fine needle biopsy. In 9 of the 12 patients, subadventitial removal of the tumor was performed and resulted in no recurrence during the mean follow-up period of > 8 yr. Although the other three patients died (cerebral infarction, myocardial infarction, and renal insufficiency), there was no evidence of recurrence. Although operation of carotid body tumors may require vascular reconstruction, it is concluded that subadventitial excision gives good prognosis. (28 refs)

- 79-0510 Bilateral Acinous Cell Tumors of the Parotid Gland.** (Eng) Nelson, D. W. (Dept. Otolaryngology, Henry Ford Hosp., Detroit, MI, 48202); Nichols, R. D.; Fine, G. *Laryngoscope* 88(12): 1935-1941; 1978.

The tenth reported case of bilateral acinous cell tumors of the parotid gland is presented. A 59-yr-old woman presented with a relatively pain-free swollen left parotid gland of 6 mo duration. Biopsy revealed an acinic cell carcinoma, and this diagnosis was confirmed upon left total parotidectomy. One year later, she complained of painful swelling in the right parotid gland. No discrete tumor was identified upon physical examination. After continued pain-free enlargement of the gland over the next year, a biopsy was performed. It revealed a diffuse acinic cell carcinoma that was removed by total right parotidectomy. Both tumor specimens were similar grossly and microscopically. The cut surface revealed many discrete, irregular, moderately firm tan nodules 0.2-1.0 cm in diameter replacing most of the parotid gland. These tumors, which arise from pluripotent duct cells or the secretory cells of the salivary gland acini, are weakly malignant. Microscopically, they bear a striking resemblance to the normal acinous tissue of the parotid. The cells are in close contact with small amounts of vascular stroma, and they are often arranged as well-formed acini with an abundant basophilic granular cytoplasm. The cells may be round or polygonal with small, dark, eccentric nuclei. Nucleoli are usually indistinct and mitotic figures uncommon. The clear cell component is stained poorly or not at all with hematoxylin-eosin but may be stained with PAS. The tumors do not exhibit histologic criteria by which local aggressive or metastatic behavior can be predicted. (19 refs)

- 79-0511 The Pathogenesis of Cancer (Meeting Abstract).** (Eng) Louis, C. J. (Dept. Pathology, Univ. Melbourne, Austin Hosp., Heidelberg, Victoria, Australia). *Pathology* 10(4): 392; 1978. (no refs)

- 79-0512 Giant-Cell Tumor of the Maxilla. Report of a Case.** (Eng) Ajagbe, H. A. (Dept. Dentistry, Univ. Coll. Hosp., Ibadan, Nigeria); Samuel, I.; Daramola, J. O. *Oral Surg* 46(6): 759-764; 1978.

A case is reported of a giant cell tumor arising in the right mandible of a 5-yr-old boy. The patient was seen for a mass of 4 months' duration that extended to the infraorbital regions superiorly, the soft palate posteriorly, and expansively anteriorly. An incisional biopsy identified the mass as a giant-cell, grade II tumor. The tumor was subsequently removed in a large piece through a Weber-Fergusson incision, and after 23 mo the recovery remains uneventful. Pathologically, the 6 x 5 x 5-cm fleshy tumor was composed of maxillary tissue (60 g), spongy in appearance, light brown in color, and gritty to the touch. There was also a nodular mass (18 g) present, consisting of granular, gritty brown tissue containing occasional bone spicules. Histologically, the tumor was composed of a spindle-shaped stroma in which multinucleated giant cells were found. The 5 to 50 nuclei per giant cell showed a mild degree of pleomorphism and scattered mitotic figures, and the giant cells in general stood out distinctly from the surrounding stroma. No areas of hemorrhage or hemosiderin-laden macrophages were present in the stroma. In differential diagnosis, hyperparathyroid function, osteogenic sarcoma, and epulides must be ruled out. (11 refs)

- 79-0513 Fibrous Histiocytoma of the Head and Neck: A Case Report.** (Eng) Hutchinson, J. C. (1753 W. Congress Parkway, Chicago, IL, 60612); Friedberg, S. A. *Laryngoscope* 88(12): 1950-1955; 1978.

A case report of a recurring malignant fibrous histiocytoma (FH) of the submandibular gland is reported, and 35 literature cases of FH originating in various deep structures of the head and neck (excluding the orbit) are reviewed. A 62-yr-old woman underwent enucleation of a left submandibular gland tumor that was considered a benign FH, although malignancy could not be ruled out. A recurrence at the same site 29 mo later was also enucleated, but this lesion was considered a malignant FH. Approx 1 yr later, a segmented mandibulectomy was performed to remove a 3-cm malignant FH that had arisen over the midportion of the body of the left mandible. Six months later, a similar 3-cm mass was removed from the midportion of the left cheek, and 6 mo after this surgery, three isolated metastatic nodules were resected from the right lung. The patient remains clinically free of disease 15 mo after the last recurrence. FH are composed of fibrocytes and histiocytes in varying ratios, and they may also possess tumor

giant cells. Synonyms for this tumor are numerous, and xanthofibroma, fibroanthoma, and dermatofibroma are included among the 14 listed. One percent prove to be malignant, and 25% of these metastasize. Diagnosis of malignancy must be made by clinical (metastases) rather than histologic means. Electron microscopy has not proved useful in determining malignancy. In the head and neck region, the FH appears to be more common in men by a ratio of 3:1. Most patients are in the fifth decade, but the age range is wide. (14 refs)

- 79-0514 Sinus Histiocytosis with Massive Lymphadenopathy (Rosai-Dorfman Disease): Report of a Case with Respiratory Tract Involvement.** (Eng) Carpenter, R. J. (Dept. Otorhinolaryngology, Mayo Clinic and Mayo Foundation, 200 First St., S. W., Rochester, MN, 55901); Banks, P. M.; McDonald, T. J.; Sanderson, D. R. *Laryngoscope* 88(12): 1963-1969; 1978.

A case of sinus histiocytosis with massive lymphadenopathy (SHML) (Rosai-Dorfman disease) in a patient with extensive nasal and tracheobronchial involvement and massive cervical lymphadenopathy is presented. A 44-yr-old Caucasian woman was admitted with complaints of nasal obstruction, stridor, and recurrent cervical adenopathy. Indirect laryngoscopy upon admission showed circumferential subglottic narrowing due to a band of erythematous granular tissue. Lymph node, tracheal, and nasal biopsies indicated submucosal infiltration by lymphoid cells and histiocytes engulfing cellular debris. Capsular fibrosis, sinusoid enlargement, and dense plasmacytosis were also present in the lymph nodes, and the diagnosis was amended to SHML. Four months later, the subglottic narrowing and cervical node enlargement had progressed, and bilateral parotid swelling was first noted. Erythematous, granular-appearing polypoid tissue that extended from the immediate subglottic area downward for 3-4 cm and narrowed the lumen to about 50% normal diameter was identified upon direct laryngoscopy and bronchoscopy. Similar polypoid masses were found on the right wall of the midtrachea, on the anterior wall of the distal trachea, and in the right main bronchus (occluded 40%). Stridor and dyspnea were immediately relieved upon removal of this tissue. However, obstruction recurred 3 mo later. It was successfully treated by chlorambucil (6 mg/day) and prednisone (100 mg every other day), even though the disease was proved histologically to be nonneoplastic. The symptoms disappeared rapidly on this regimen and the patient currently (5 mo later) feels well. Concomitant upper and lower airway involvement in addition to cervical adenopathy is an unusual finding in SHML. (11 refs)

- 79-0515 Characteristics and Diagnostic Approaches in the Detection of Nonapparent Bronchogenic Carcinoma.** (Eng) Hofner, W. (Dept. Radiology, Second Medical Univ. Clinic, Garnisongasse 13, A-1090 Vienna,

Austria); Kuester, W.; Seidl, G. *Radiol Clin (Basel)* 47(6): 412-422; 1978.

Three case reports demonstrate that a negative chest x-ray does not exclude a bronchogenic carcinoma. However, tomography allows early detection of small tumors in the hilum or tumors hidden in the mediastinal shadow in the absence of parenchymal changes. (20 refs)

- 79-0516 Congenital Solitary Cysts of the Liver and Spleen.** (Eng) Williamson, R. C. (Univ. Dept. Surgery, Bristol Royal Infirmary, Bristol, England); Ramus, N. I.; Shorey, B. A. *Br J Surg* 65(12): 871-876; 1978.

Three symptomatic cases of congenital solitary cyst are reported, one in the liver (49-yr-old woman) and two in the spleen (18- and 30-yr-old women). The incidence, pathology, presentation, diagnosis, and complications of these cysts are summarized. One complication of the hepatic cysts is malignant change. (43 refs)

- 79-0517 Electron Microscopic Findings in a Malignant Hepatoma after Oral Contraception.** (Ger) Hatzibujas, J. (Institut für Pathologie I, Bundesknappschaft Am Deimelsberg 34A, D-4300 Essen 14, W. Germany); Ueberberg, H.; Stoldt, R.; Breining, H. *Z Gastroenterol* 16(10): 616-624; 1978.

The results of an electron microscope (EM) study of a hepatocellular carcinoma found in a 24-yr-old woman are described. Preoperatively, the clinical, laboratory, and histological findings suggested chronic aggressive hepatitis. The patient had been taking an ovulation-inhibiting contraceptive for 5 yr, until only a few wk before surgery. After biopsy, diagnosis, and surgical removal of the tumor, the patient died from bleeding from a hepatic vein. EM study showed numerous mitochondria and few other organelles in the tumor cells. Glycogen was mostly extracellular. Lysosome membranes showed myelin-like residual bodies. Deep invagination was the most marked nuclear change. Endoplasmic reticulum (ER), mitochondria, and glycogen were found within the invaginated spaces. Finger-like nuclei containing ER, ribosomes, glycogen, and lipid drops were also found. The mitochondria were swollen, with rudimentary cristae and a homogenous matrix. They had polymorphic forms and were often interdigitated. Although many of these characteristics, such as invagination of the nuclei, have been found previously in tumors, the EM findings cannot be considered specific for malignant tumors of the liver. In contrast to several other reports, no giant mitochondria with paracrystalline inclusions were found. (18 refs)

- 79-0518 Early Endoscopic Features of Stomach Cancer and Its Mode of Growth.** (Eng) Hisamichi, S.

(Cancer Detection Center, Miyagi Cancer Society, Kamisugi 6-Chome, 2-81, Sendai 980, Japan); Shirane, A.; Sugawara, N.; Asaki, S.; Yanbe, T.; Ito, S.; Funada, K.; Hatori, S.; Ikeda, T.; Ito, Y.; Masuda, Y.; Ooshiba, S. *Tohoku J Exp Med* 126(3): 239-246; 1978.

Morphologic changes and early endoscopic features of 14 cases of advanced and 27 cases of early stomach cancer were studied. Thirty-five patients were men, 6 were women. Fifteen cases had infiltrated the gastric mucosa (mean age 57.3), 12 had infiltrated the submucosa (58.5), 9 had infiltrated the muscularis propria or had extended to the submucosa (59.0), and 5 had infiltrated the serosa or more deeply (49.8). The earliest endoscopic signs consisted of redness (12 cases), small polypoid lesions (7 cases), and flat mucosa with slight unevenness and small depressed lesions (a few cases). Redness or a small depressed lesion tended to develop into the superficial and depressed or excavated types of cancer, but small polypoid lesions tended to develop into the superficial, elevated type. The features of early stomach cancer could not be used to determine the type of advanced cancer that would develop. The av time from first endoscopic finding to the diagnosis of early cancer was 44 mo, and the av time from early cancer to advanced disease was 33.4 mo. There was no difference in rate of progression between differentiated vs undifferentiated cancers or protruding vs depressed types. Using a least squares method, the size of the cancer lesion was correlated with observation period for advanced disease but not early disease. (31 refs)

79-0519 Morbid Changes of the Mandible in Familial Polyposis of the Colon. (Eng) Shoji, K. (Third Dept. Internal Medicine, Tohoku Univ. Sch. Medicine, Sendai 980, Japan); Watanabe, H.; Goto, Y.; Yamada, N. *Tohoku J Exp Med* 126(3): 289-293; 1978.

Morbid changes of the mandible were investigated in 11 patients (9 men, 2 women aged 15-48 yr) with familial polyposis coli (FPC) admitted to a Japanese hospital over the past 15 yr. Ten patients and six unaffected family members underwent orthopantomography of the mandible: the 11th patient had died at age 23 of cancer of the sigmoid colon, and radiographic and histological studies were made of the excised mandible. Sclerotic masses of the mandible were found in 10/11 patients; in some patients, they were also found in the maxilla. The number of sclerotic masses ranged from 2 to 11, and they were associated with odontomas in 2 patients and impacted teeth in 1. A radiographic study of the excised mandible of the 11th patient revealed 11 sclerotic masses, each approx 5 mm in diameter, and 1 impacted tooth. Upon buccolingual cross section of the mandible in the canine area, central osteomas composed of mature lamellar tissue of bone were identified. Sclerotic masses were also found in 2/6 unaffected family members and in 7/60 other dental patients and 0/10 colonic adenoma patients chosen as controls. These results support the view that Gardner's syndrome and FPC are

etiologically identical lesions with minor differences due to variable gene expression. (6 refs)

79-0520 Malignant Potential of Chronic Ulcerative Colitis. Preliminary Report. (Eng) Nugent, F. W. (Dept. Gastroenterology, Lahey Clinic Foundation, 605 Commonwealth Ave., Boston, MA, 02215); Haggitt, R. C.; Colcher, H.; Kutteruf, G. C. *Gastroenterology* 76(1): 1-5; 1978.

In an attempt to further define the histologic and clinical risk factors of the premalignant state of ulcerative colitis (UC), a two-part study was undertaken comprising a retrospective analysis of patients with UC and carcinoma and a prospective analysis of patients with long-standing UC. Of 23 patients with colon carcinoma and chronic UC, 22 exhibited dysplasia of colonic epithelium remote from the cancer. The prospective evaluation reviewed clinical data as well as rectal and colonoscopic biopsy specimens on 36 patients with chronic UC, 12 with Crohn's colitis, and 12 with miscellaneous disorders. Of the patients with chronic UC, 8 had dysplasia, 6 have had colectomy, and 2 of the latter had carcinoma. No patient without chronic UC had dysplasia. It is concluded that patients with chronic UC should have periodic rectal and colonoscopic biopsies, and those demonstrating moderate to severe dysplasia require colectomy because of the increased risk of colon carcinoma. (15 refs)

79-0521 Cancer of the Rectum Following Colectomy and Ileorectal Anastomosis for Ulcerative Colitis. (Eng) Baker, W. N. (Surgical Unit, London Hosp., London E1 1BB, England); Glass, R. E.; Ritchie, J. K.; Aylett, S. O. *Br J Surg* 65(12): 862-868; 1978.

The case records of 384 patients treated for ulcerative colitis by colectomy and ileorectal anastomosis by one surgeon between 1952 and 1976 were reviewed. Of the 374 who have been followed-up (for periods up to 23 yr), 22 are known to have developed rectal carcinoma. Within 10 yr of the operation, no rectal carcinoma was found in 3,534 patient-yr. The risk was 1 in 185 patient-yr between the 10th and 20th yr and 1 in 115 patient-yr between the 20th and 30th yr. The overall risk was $6 \pm 2\%$ at 20 yr and $15 \pm 4\%$ at 30 yr. Stress is placed on the need to meticulously follow up all cases. It is suggested that dysplasia in rectal mucosal biopsies may identify the patient at high risk and facilitate rectal excision before the onset of rectal carcinoma. (45 refs)

79-0522 Oestrogen Receptor Content of Primary Breast Tumours as a Prognostic Indicator of Early Recurrence (Meeting Abstract). (Eng) Maynard, P. V. (Tenovus Inst. Cancer Res., Welsh Natl. Sch. Medicine, Cardiff, CF4 4XX, Wales); Davies, C. J.; Elston, C. W.; Blamey,

R. W.; Griffiths, K. *J Endocrinol* 79(2): 50P-51P; 1978. (3 refs)

79-0523 Metastatic Bone Involvement in Gynecological Malignancies. (Eng) Brufman, G. (Dept. Oncology, Sharett Inst., Hadassah Univ. Hosp., POB 499, Jerusalem, Israel); Krasnokuki, D.; Biran, S. *Radiol Clin (Basel)* 47(6): 456-463; 1978.

The case reports of four women in whom metastatic bone involvement in a gynecological malignancy was diagnosed ante mortem are presented, and similar cases from the literature are reviewed. An osteolytic lesion in the lesser trochanter of the right femur was identified in a 69-yr-old woman while she was undergoing surgery for endometrial carcinoma. She was successfully treated with radiation and hormone therapy. Case 2 was a 57-yr-old woman who responded well to cobalt-60 radiation and intrauterine radium application for a Stage IIb squamous cell carcinoma of the cervix. Three years later, an osteolytic lesion in the left sacroiliac joint was successfully treated with radiation therapy. Case 3, a 43-yr-old woman, underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy for a mesonephric carcinoma of the ovary. Three years later, an osteolytic lesion in the right femur plus a periosteal reaction appeared that were managed with radiation + chemotherapy. The fourth case, a 46-yr-old woman, underwent simple vulvectomy for squamous cell carcinoma of the vulva, and 8 mo later an osteolytic lesion was noted in the lower left tibia. Radiation therapy produced a good response, but 5 mo later the patient was rehospitalized for a pathological fracture of the left tibia with accompanying multiple metastatic lesions of the skin of the abdomen and both legs. Gynecological tumors ordinarily spread through the lymphatic system, and only in the most advanced cases is hematogenous spread noted, usually at necropsy. Therefore, these findings of hematogenous spread to bone in living patients are unusual. (13 refs)

79-0524 Cytologic Changes of Cervical Cancer According to the Degree of Invasion. (Eng) Yajima, A. (Dept. Obstetrics and Gynecology, Tohoku Univ. Sch. Medicine, Sendai 980, Japan); Teshima, K.; Noda, K. *Tohoku J Exp Med* 126(13): 295-299; 1978.

Cervical scrapings from 86 patients with carcinoma in situ (A), 91 with early invasive cancer (stromal invasion ≤ 5 mm B), and 50 with advanced cancer (C) were examined microscopically and analyzed numerically, and the results were used to try to determine the morphologic extent of the lesions. The number of malignant cells in the preparation increased with the extent of the lesion (from 31.4% to 65.9% to 92%). The occurrence of irregularly distributed, coarsely granular chromatin increased with the progression A to B to C. Anisocytosis, inclusion cells, and cellular detritus all likewise increased with increasing invasiveness, and in general these

patterns continued on a more specific scale when early invasive cancer was subdivided into four categories based on depth of invasion (1, 2, 3, or 5 mm). The ratio of malignant cells in the deep layer to malignant cells in the entire layer was 81% in A, 61% in B, and 55% in C. There was also an increase in the ratio of malignant cells to dysplastic cells with progression of the cancer. Hyperchromatism was not a good indicator of malignancy, as 89.5% of A and 100% of B and C cells had hyperchromatic nuclei. (18 refs)

79-0525 Ultrastructure of Adenocarcinoma of the Uterine Cervix (Meeting Abstract). (Eng) Okudaira, Y. (Dept. Gynecology, Center Adult Diseases, Osaka, Japan); Hayakawa, K.; Matsui, Y. *J Electron Microsc (Tokyo)* 27(4): 384; 1978. (no refs)

79-0526 Fine Structure of Human Chorionic Tumor. (I) Destructive Mold--with Special Reference to the Relation Between the Tumor Cells and the Myometrial Cells (Meeting Abstract). (Eng) Hirasawa, T. (Dept. Obstetrics and Gynecology, Sapporo Medical Coll., Sapporo, Japan); Hashimoto, M. *J Electron Microsc (Tokyo)* 27(4): 384; 1978. (no refs)

79-0527 Ultrastructural Studies of Experimental Yolk Sac Tumors in the Rat (Meeting Abstract). (Eng) Teshima, S. (Dept. Pathology, Hokkaido Univ. Sch. Medicine, Sapporo, Japan); Nakamura, K.; Aizawa, M.; Sakashita, S. *J Electron Microsc (Tokyo)* 27(4): 384; 1978. (no refs)

79-0528 The Prognostic Significance of Cytologic Differentiation Grades in Estrogen-treated Prostate Carcinoma. Course Control of 496 Carcinoma Patients Treated with Estrogen for 5 Years. (Ger) Faul, P. (Urologische Abteilung, Stadt Krankenhaus, Bismarckstrasse 23, D-8940 Memmingen, W. Germany); Schmiedt, E.; Kern, R. *Urologe [A]* 17(6): 377-381; 1978.

The cytologic differentiation grades of 496 estrogen-treated prostatic carcinoma patients (av age 68-69 yr) correlated with their prognosis. Av survival time was 6.9 yr for those with highly differentiated tumors, 2.6 yr for those with poorly differentiated tumors, and 1.9 yr for those with anaplastic carcinomas. The short survivals of those with the latter two

types of carcinoma suggest that the use of estrogens in these patients should be questioned. (28 refs)

79-0529 Cytologic Grading of Prostatic Carcinoma. (Ger) Voeth, C. (Pathologisches Institut, Städtisches Krankenhaus Neu-Perlach, Oskar-Maria-Graf-Ring 51, D-8000 Munich 83, W. Germany); Droese, M.; Steuer, G. *Urologe A* 17(6): 367-370; 1978.

The cytological differentiation grade (Esposti's method) was compared with the histological differentiation grade (Dhoms' method) for 92 prostate carcinomas. Agreement was found in 43 cases. The cytologic grading was reproducible in 60.9% of the cases; in 39.1%, the difference between the first and second evaluation was one grade. The omission of cellular atypia from the cytologic criteria, leaving only microglandular structure and cell dissociation, is suggested to make cytologic grading less subjective and more reproducible. (9 refs)

79-0530 Regulation of Tumor Metastasis in Nude Mice (Meeting Abstract). (Eng) Klein, A. S. (Dept.

Genetics, Albert Einstein Coll. Medicine, Bronx, NY); Kim, U.; Shin, S. *J Cell Biol* 79(2, part 2): 90a; 1978. (no refs)

See also:

- * (Rev.): 79-0039, 79-0041, 79-0042, 79-0043, 79-0044, 79-0062, 79-0063, 79-0071, 79-0072, 79-0073, 79-0074, 79-0075, 79-0076, 79-0077, 79-0078, 79-0079, 79-0080, 79-0081, 79-0082, 79-0083, 79-0084, 79-0085, 79-0086, 79-0093, 79-0095.
- * (Chem.): 79-0101, 79-0103, 79-0107, 79-0108, 79-0111, 79-0112, 79-0122, 79-0128, 79-0130, 79-0133, 79-0141, 79-0171, 79-0174, 79-0180, 79-0198, 79-0199, 79-0204, 79-0213, 79-0221, 79-0227, 79-0234, 79-0236, 79-0242, 79-0265, 79-0274, 79-0300, 79-0309, 79-0310, 79-0312, 79-0315, 79-0316.
- * (Phys.): 79-0331, 79-0335, 79-0336, 79-0342, 79-0343, 79-0344, 79-0345, 79-0346, 79-0347, 79-0349, 79-0354, 79-0378, 79-0379, 79-0380, 79-0389, 79-0390.
- * (Viral): 79-0405, 79-0418, 79-0420, 79-0430, 79-0439, 79-0461.
- * (Immun.): 79-0478, 79-0482, 79-0489.
- * (Epid.-Biom.): 79-0531, 79-0533, 79-0534, 79-0539, 79-0544, 79-0545, 79-0546, 79-0548, 79-0549, 79-0556, 79-0558, 79-0561, 79-0579, 79-0581.

EPIDEMIOLOGY AND BIOMETRY

- 79-0531 Mediastinal Tumours. A Follow-up Study of 208 Patients.** (Eng) Luosto, R. (Dept. Thoracic and Cardiovascular Surgery, Univ. Central Hosp., Helsinki, Finland); Koikkalainen, K.; Jyrälä, A.; Franssila, K. *Scand J Thorac Cardiovasc Surg* 12(3): 253-259; 1978.

During the period 1954-1973, 208 patients were referred to a Finnish hospital for treatment of mediastinal tumors. Forty-nine patients had malignant tumors (24%), 86 benign tumors and 73 nonneoplastic lesions. The most common histologic types were neurogenic tumors and malignant lymphomas, followed by thymomas and teratomas. Most nonneoplastic lesions were cysts. Thirty-five percent of the malignant tumors were asymptomatic, compared with 65% of the benign tumors and 66% of the nonneoplastic lesions. The most common symptom was pain, which occurred in one-fifth of the patients. The most useful diagnostic method was chest x-ray examination. However, a final diagnosis could usually be made only at operation. Thirteen malignant tumors were excised radically, 18 palliatively, and 18 were only biopsied. Almost all benign tumors were radically excised. Forty-four patients received postoperative radiation therapy and 6 received chemotherapy. The hospital mortality was 8.2% for patients with malignant tumors and 1.9% for those with benign tumors. At the end of the follow-up period, which ranged from 2 to 21 yr (median 10.3 yr), 41% of the patients with malignant tumors were alive. Two patients with benign tumors had died of an apparently malignant change in a neurofibroma. (15 refs)

- 79-0532 Estrogen Replacement Therapy and Endometrial Carcinoma.** (Eng) Rauramo, L. (Dept. Obstetrics and Gynaecology, Turku Univ. Central Hosp., Hämeenkatu 4, SF-20520 Turku 52, Finland). In: *Front Horm Res* 5: 117-125; 1978.

History of estrogen use was investigated by interview in 317 Finnish patients treated for endometrial cancer between 1970 and 1976 and in 304 healthy controls matched for age, wt, and social class. Only 9% of the cancer patients had ever taken estrogens, and the mean duration of use was 8 mo (range, 1-46 mo), but 19% of the control women reported taking estrogens for an av of 15 mo (1-84 mo). One incidental finding that was interesting concerned the use of other medication. When asked if they had been regularly taking other medication at the time of cancer diagnosis, 68% of cancer patients replied affirmatively. Most were being treated for hypertension (26%) and for congestive heart failure (22%); 6% were receiving analgesics. Only 37% of controls were

receiving other medication at a comparable point in time, with 14% being treated for hypertension. This study did not demonstrate an association between estrogen use and endometrial carcinoma, contrary to recent studies in the US (and other countries). This discrepancy may be due to qualitative and quantitative differences in the estrogen replacement therapies. (6 refs)

- 79-0533 Cancer Risk in Women with Uterine Myoma.** (Ger) Grosse, H. (Pathologisch-Anatomische Abteilung der Frauenklinik, Bezirkskrankenhaus Stralsund, Billrothstr. 22, DDR-23 Stralsund, E. Germany); Hohlbein, R.; Suffert, D.; Feiste, V. *Zentralbl Gynaekol* 100(10): 642-649; 1978.

The cancer risk of women with myoma was studied in an autopsy series and compared with controls (autopsy series without myoma or with past hysterectomy). In the autopsy series of women without myoma, gastric cancer was by far the most frequent tumor, followed by carcinomas of the intestines, bile ducts, and uterine cervix. Among the autopsied patients with past hysterectomy, breast cancer and carcinomas of the bile ducts, intestines, and stomach are most frequent. Breast carcinoma was most frequent in the autopsy series with myoma, followed by carcinomas of the stomach, bile ducts, intestines, and endometrium. Compared with the controls, the myoma patients showed a slightly increased incidence of adipositas, hypertension, lung embolism and myocardial infarction. Cancer was found in 336/1,306 autopsied women with myoma (25.7%), in 170/577 hysterectomized patients (29.5%), and in 2,472/8,243 controls (30%), ie, the findings do not indicate any increase in the cancer risk of patients with uterine myoma. Malignant transformation of the uterine myoma was seen in 0.7% of all cases. (52 refs)

- 79-0534 Endometrial Pathology and Its Relation to Estrogen Therapy in Patients with Hypogonadism.** (Eng) Rosenwaks, Z. (Dept. Pediatrics, Johns Hopkins Univ. and Hosp., Baltimore, MD, 21205); Urban, M. D.; Wentz, A. C.; Lee, P. A.; Parmley, T. H.; Migeon, C. J.; Jones, G. S.; Woodruff, J. D. *Pediatrics* 62(6, part 2, Suppl): 1184-1188; 1978.

The relationship between estrogen (EG) therapy and endometrial histology was investigated in 43 hypogonadal patients (av age 24.3 yr) receiving daily cyclic exogenous EG therapy for an av of 7.2 yr due to some variant of gonadal dysgenesis (41) or hypopituitarism (2). The therapy consisted of conjugated EG's (36 patients), conjugated EG's + diethyl-

stilbestrol (DES: 5), or DES only (2). Forty patients were receiving sequential EG/progesterone therapy, 3 EG therapy only. There were seven abnormal biopsies: six cases of benign cystic hyperplasia (BCH) and one of atypical hyperplasia. In the three BCH patients for whom data were available, the condition improved with reduced EG dose. The condition of the atypical hyperplasia patient, who initially refused surgical treatment, worsened; an epidermoid adenocarcinoma was identified upon subsequent hysterectomy. She had received the largest lifetime EG dose (20,320 mg) and had one of the longest treatment durations (19 yr). The patients were shown to be at statistically greater risk for abnormal endometrial biopsy findings if they had received a lifetime dose of conjugated EG's $\geq 2,500$ mg, the durations of EG therapy was > 7 yr, and the dose of conjugated EG's at biopsy was > 1.25 mg/day. The total lifetime progesterone dose was not correlated with endometrial pathology, nor was the occurrence of abnormal bleeding. (21 refs)

- 79-0535 Cancer of Ovary in Israel (1966-1971).** (Eng) Schenker, J. G. (Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., Jerusalem, Israel); Mazzor, M. *Gynecol Oncol* 6(5): 397-410; 1978.

The epidemiology and clinical course of carcinoma of the ovary in Israel during 1966-1971 were studied. The incidence of primary carcinoma of the ovaries was 16.2/100,000 in women aged > 15 yr. Seventy-five percent of the patients were aged 45-74 yr. Women of European/American origin had three- to fourfold higher incidence of ovarian cancer than those of Asian/African background. Fifty-one percent of the patients were diagnosed at an advanced stage of the disease, with only 14.5% being diagnosed at Stage 1A. The most frequent tumor was serous cystadenocarcinoma (41%); there was no significant predilection for involvement of one ovary or the other. The most frequent presenting symptoms were lower abdominal pain, abdominal enlargement, vaginal bleeding, and acute abdominal symptoms. The 5-yr survival rate was 22.2%, the 3-yr survival rate 28%. Factors affecting prognosis were age of the patient, presenting symptoms, clinical stage of the disease at diagnosis, histology of the tumor, and type of treatment. (24 refs)

- 79-0536 Pituitary Adenomas and Oral Contraceptives: A Case-Control Study (Meeting Abstract).** (Eng) Coulam, C. B. (Dept. Obstetrics and Gynecology, Mayo Clinic, Rochester, MN); Annegers, J. F. *Fertil Steril* 30(6, Suppl): 736; 1978. (no refs)

- 79-0537 Possible Protection from Breast Cancer by Oral Contraceptives (Meeting Abstract).** (Eng) Gambrell, R. D. (Dept. Obstetrics and Gynecology, Wilford Hall United States Air Force Medical Center, Lackland Air Force

Base, TX); Massey, F. M.; Castaneda, T. A.; Boddie, A. W. *Fertil Steril* 30(6, Suppl): 754-755; 1978. (no refs)

- 79-0538 Oral Contraceptives and Breast Disease in Premenopausal Northern Albertan Women.** (Eng) Lees, A. W. (Cross Cancer Inst., Univ. Alberta, Alberta, Canada); Burns, P. E.; Grace, M. *Int J Cancer* 22(6): 700-707; 1978.

A prospective study on oral contraceptive use and breast disease in northern Alberta is presented. All women aged 30-49 yr who were examined at one diagnostic breast clinic were included in the study; 301 women with malignant breast cancer, 696 with benign breast disease confirmed by biopsy, and 548 women who did not receive a biopsy because there was no apparent breast disease were evaluated in terms of relative risk of breast cancer due to history of oral contraceptive use. All women selected were classified as recent users (REU) if contraceptives had been used in the past year. Otherwise, they were classified as former users (FRU). Length of use was divided into categories of ≤ 12 mo (S), 13-59 mo (M), or ≥ 60 mo (L). Considering duration of use only, the relative risk (RR) of developing breast cancer was significantly decreased in S users (0.6), increased to 1.4 among M users, and unchanged (1.0) in L users compared to never-users. When recent or former use is considered, the RR was ≥ 1 for all REU, while among FRU, the RR was reduced to 0.3 for S users and to 0.5 for L users but was 1.3 for M users. When the presence of a previous biopsy was considered, REU had a significantly increased RR of 5.0, while users of L duration had an increased RR of 9.2 (also significant) and M users had an increased RR of 2.3. In the M group without biopsy the RR was increased to 1.3, whereas in the S and L groups it was < 1.0 , tending to support theories that preexisting subclinical breast cancer is induced by oral contraceptives after several months of use and is only identified in ensuing years. (38 refs)

- 79-0539 Urinary Bladder Carcinoma in Biopsy Material During the Last 50 Years: Changes in Sex and Age Distribution and Frequency.** (Ger) Schubert, G. E. (Pathologisches Institut der Kliniken, Stadt Wuppertal, Arrenberg Strasse 20-56, D-5600 Wuppertal 1, W. Germany); Steinert, M. *Urologe A* 17(6): 361-366; 1978.

The frequency, sex, and age distribution of the urinary bladder biopsies performed at a clinic in Wuppertal, W. Germany, from 1927 to 1957 (T1) and from 1972 to 1976 (T2) were compared. T1, 234 bladder carcinomas (BC) were found among 440 biopsies; during T2, 655 BC were found among 1,634 bladder biopsies. The male:female ratio was 3.4 in T1 and 2.6 in T2. The age distribution curve for T1 showed a peak at 56-60 yr and a secondary peak at 66-70 yr. The youngest patients were 26-30 old. In contrast, the curve for T2 had a sharp peak at 66-70 yr, and the youngest patients

were 31-35 yr old. The proportion of transitional cell BC was 81.2% in T1 and 80.0% in T2; that of squamous cell BC was 2.8% in T2 and 5.1% in T1. Papillomas were found in 14% of all bladder biopsies in T1 vs 32% in T2. The fraction of well-differentiated BC increased in T2 compared to T1. The incidence of BC found in bladder biopsies climbed from 31.2% in 1972 to 52.5% in 1976. It seems doubtful that indications for biopsy have changed enough to account for this increase. No clear relationship between occupation and BC was found. (22 refs)

- 79-0540 Volatile Nitrosamines in Some Traditional Southern Chinese Food Products.** (Eng) Huang, D. P. (Medical and Health Dept., Inst. Radiology and Oncology, Queen Elizabeth Hosp., Kowloon, Hong Kong, China); Ho, J. H.; Gough, T. A.; Webb, K. S. *J Food Safety* 1(1): 1-6; 1977.

Due to the previous association seen between nasopharyngeal carcinoma and consumption of Cantonese salted fish in Southern Chinese populations attributed to the presence of nitrosamines, other salted food products common to the Southern Chinese diet were also tested for these compounds by gas chromatography and high resolution mass spectrometry. Pork sausage, goose-liver sausage, salt-dried beans, soya bean paste, soy, shrimp paste, oyster sauce, soyabean curd, salt-dried egg yolk, fish sauce, anchovies, croaker, red snapper, white herring, yellow croaker, and mixed fish heads were purified, extracted, concentrated and tested for the presence of seven different nitrosamines. Only N-nitrosodimethylamine was present in two samples of anchovies, one sample of croaker, three samples of white herring, and two samples of yellow croaker. The levels of this nitrosamine in these foods were no higher than those encountered in European cultured meats. No other volatile nitrosamines were detected in any other salted foods tested, a total of 34 different samples. This study does not rule out the possibility that nitrosamines are formed from these foods either during cooking or after ingestion. (19 refs)

- 79-0541 Nitrate Nitrogen Levels in Drinking Water of Urban Areas with High- and Low-risk Populations for Stomach Cancer: An Environmental Epidemiology Study.** (Eng) Zaldivar, R. (International Res. Group Cancer Epidemiology Human Ecology, 5055 N.W. 7th St, Suite 606, Miami, FL, 33126); Wetterstrand, W. H. *Z Krebsforsch* 92(3): 227-234; 1978.

A correlation study between mean nitrate levels (ppm) in drinking water samples (total 1,389) of Chilean urban areas and age-adjusted death rates per 100,000 population from stomach cancer, by province or region and sex, was made. Drinking water samples from all provinces had a weighed mean of 1,446 ppm, with a range of 0.00-30.00 ppm. Nitrate levels showed a positive but not significant association with

male death rates. The correlation coefficient was +0.0335. Similarly, the levels exhibited a positive but not significant correlation with female death rates ($r = +0.0486$). When nitrate levels and male ($r = 0.1367$) or female ($r = +0.1143$) death rates were studied by region, positive but insignificant correlations were detected. Using Cochran's approximation, mean nitrate levels in drinking water samples from six provinces with 50% of the Chilean population decreased from 1,835 in 1953-1955 to 1,291 ppm in 1973-1975, but there was no significant difference ($t = 1.32$) between the two values, except in samples from Santiago Province ($t = 2.11$, $p < 0.05$). Provinces (south central area) with the highest gastric cancer mortality rates in the world for women (up to 40.8/100,000), and ranking second for men (up to 84.1/100,000), exhibited a low mean level (0.825 ppm). (25 refs)

- 79-0542 The Agricultural Use of Nitrate Fertilizers (Tons of N) in Provinces of Chile with High- and Low-risk Populations for Gastric Carcinoma.** (Eng) Zaldivar, R. (International Res. Group Cancer Epidemiology & Environmental Hygiene, 5055 N.W. 7th St., Suite 606, Miami, FL, 33126). *Bull Cancer (Paris)* 65(3): 365; 1978.

Data concerning the use of nitrate fertilizers in Chilean provinces having high and low incidences of stomach carcinoma are presented. Between 1945 and 1969, provinces with the highest incidences of stomach cancer also used the greatest amounts of nitrate fertilizers, while provinces with the lowest rates used the least amounts. (6 refs)

- 79-0543 Schistosomiasis Japonica (Katayama's Disease) and Cancer of the Gastrointestinal Tract, with Special Reference to the Presence of the Fluke Egg and Cancer Development.** (Jpn) Okamoto, T. (Fukuyama Natl. Hosp., Fukuyama-shi, Hiroshima Prefecture 720, Japan). *Gan No Rinsho* 24(8): 761-765; 1978.

Among 40 patients with schistosomiasis japonica (Katayama's disease) detected at the Fukuoka National Hospital, Japan, from 1962 to 1977, 21 also had cancer of the gastrointestinal tract (17 had stomach cancer, 4 intestinal cancer). Fourteen of the stomach cancers and all four intestinal cancers (which arose in papillae (2), sigmoid colon (1), and rectum (1)) were well-differentiated papillotubular adenocarcinomas. Fluke eggs were detected in tumor tissues in 10 of the stomach cancers and 3 of the intestinal cancers; 11 of these 13 tumors were well-differentiated papillotubular adenocarcinomas. In some patients intestinal metaplasia was recognized in the fluke-egg-containing gastric mucosa in the vicinity of the tumor. Benign elevated lesions (polyps and atypical epithelium) were observed in the stomach of 9 patients and in the large intestine of 5 patients. Malignant transformation of these benign lesions was seen in some cases. The results suggest that the gastrointestinal cancers developed in

the following steps: (1) presence of fluke eggs in gastrointestinal mucosa, (2) benign elevated lesions (polyps and atypical epithelium) and, (3) cancer. (14 refs)

- 79-0544 Cancer and "Cancer Related" Colorectal Lesions in Sao Paulo, Brazil.** (Eng) Marigo, C. (Dept. Pathology, Faculty Medical Sciences, Santa Casa Hosp., Sao Paulo, Brazil); Correa, P.; Haenszel, W. *Int J Cancer* 22(6): 645-654; 1978.

A series of 832 large bowel necropsy specimens collected in Sao Paulo, Brazil during 1973-75 were studied for the presence of colon diseases, particularly polyps, and analyzed in comparison with 5 other studied populations. Of 403 male specimens, hyperplastic polyps (HP) were found in 86, adenomatous polyps (AP) in 52, and juvenile polyps in 9. Analogous figures for 429 female specimens were 73, 52, and 9. Size and prevalence of both polyp types increased with age in both sexes. Length of colon correlated positively with risk of developing either AP or HP in this population, and the number of HP/specimen was greater than the number of AP/specimen. AP were primarily located in the ascending colon (24% of total), while the majority of HP (55%) occurred in the rectum. Racial differences were found, as the prevalence of AP in whites and blacks, respectively, was 15.6% and 9.4%, and the prevalence of HP, 26.0% and 15.6%. Furthermore, blacks did not show the predominance of AP in the proximal segments of the colon that was seen in whites. Carcinomas tended to concentrate in the descending colon and rectum, and this correlated positively with the location of HP. When compared with other colonic diseases, positive correlations were noted among the four conditions of AP, HP, diverticulosis, and hemorrhoids. Schistosomiasis did not show a significant relationship to polyps; and a consistently negative correlation was noted between AP, on the one hand and appendectomy, appendicitis, diverticulosis, and lymphoid hyperplasia on the other. These relationships are consistent with current hypotheses claiming a protective role of dietary fiber against carcinogenesis in the colon. (45 refs)

- 79-0545 Incidence of Malignant Tumors of the Stomach, Colon, Rectum and Lung and Incidence in Autopsy Material: 1900-1975, Heidelberg Area.** (Ger) Kayser, K. (Pathologisches Institut der Universitat, Im Neuenheimer Feld 220/221, D-6900 Heidelberg, W. Germany); Burkhardt, H. U.; Boschmann, W. *Virchows Arch Pathol Anat Histol* 380(2): 163-175; 1978.

A method for estimating the incidence of stomach, colon, rectum, and lung cancer from the incidences found at autopsy at the University of Heidelberg from 1900 to 1975 is described. Analysis showed that the percentage of autopsy cases has not changed significantly during this time. It was found that the incidence of stomach cancer has remained nearly constant, that of colon and rectal cancer has increased steadily,

and that of lung cancer has increased significantly since 1900. (24 refs)

- 79-0546 Autoradiographic Cytokinetics of Colonic Mucosal Hyperplasia in Mice.** (Eng) Barthold, S. W. (Section Comparative Medicine, Yale Univ. Sch. Medicine, New Haven, CT, 06510). *Cancer Res* 39(1): 24-29; 1979.

The cytokinetics of a naturally occurring hyperplastic disease of the colon in mice was determined by autoradiography and compared to kinetic changes seen by others in nonneoplastic and neoplastic colonic disease. Cell cycle parameters were determined by the fraction-labeled mitosis method. Labeling index, labeling pattern, and migration rates were also evaluated. During colonic hyperplasia, there was an increase in the variation of DNA synthesis times, resulting in prolongation of the S phase. The total cell cycle time and the G₁ phase were also prolonged. In addition, the labeling index was increased twofold, the proliferative zone was extended to include the entire crypt column and surface mucosa, and the migration rate was accelerated. These findings parallel the "atypical" cytokinetics found in human and murine neoplastic and preneoplastic disorders of the colon and may be a typical proliferative response of the mucosa to a variety of stimuli. (56 refs)

- 79-0547 The Regional Registry of Gastro-intestinal Cancer North Baden (2.2 Million Inhabitants).** (Eng) Kayser, K. (Pathologisches Institut der Universitat, Im Neuenheimer Feld 220/221, W. Germany); Burkhardt, H. U.; Jacob, W. *Virchows Arch Pathol Anat Histol* 380(2): 155-162; 1978.

The advantages, disadvantages, and experience gained from the regional gastrointestinal cancer registry in North Baden, West Germany, which is based only on histopathological data obtained from various local pathological institutes, are described. In addition, the incidences of gastrointestinal cancer in North Baden (population, 2.2 million) for the years 1971-1975 are tabulated. (16 refs)

- 79-0548 Malignant Neoplasm in Peutz-Jeghers Syndrome (2 Letters to Editor).** (Eng) Major, P. (Sidney Farber Cancer Inst., Charles A. Dana Cancer Center, Boston, MA); Ryo, U. Y. *JAMA* 240(20): 2155; 1978.

A previous conclusion that the rate of malignant transformation in Peutz-Jeghers polyps is 2%-3% is inaccurate; the 2%-3% incidence of malignancy in this syndrome refers to all digestive cancers and not only to those developing in the polyps. In a reply, it is stated that the origin of malignant neoplasms in the syndrome is difficult to document since not all polyps and tumors are given a thorough histologic exam and interpretation of the findings is subjective. (6 refs)

- 79-0549 Noncancer Deaths in Cancer and Noncancer Lineages.** (Eng) Albert, S. (Michigan Cancer Foundation, 110 East Warren Ave., Detroit, MI, 48201); Child, M. A.; Belle, S. *Am J Epidemiol* 108(5): 373-376; 1978.

To investigate whether a lineage in which at least one cancer was reported has a higher mortality in its noncancer members than does a lineage which has no cancer, family health histories of 2,411 female milk donors in a viral cancer study were collected. A lineage was defined as the parents and siblings of a parent of a subject. All together, 4,635 useable lineages of 4,822 potential lineages and 31,939 individuals were obtained for evaluation. A cancer lineage was defined as one in which at least one member was diagnosed as having cancer. Noncancer death rates were computed and expressed as deaths/100,000 person-years of exposure. Expected death rates in cancer lineages were calculated on the basis of the overall death rate in the entire population. There were 1,580 cancer lineages, of which 1,229 had only one cancer in the lineage. In all age groups of females except 45-49 yr, the noncancer death rate in the cancer lineage was significantly higher than in the noncancer lineage. Likewise, all male groups from cancer lineages, except those aged 35-44, had significantly higher noncancer death rates than did individuals from noncancer lineages. Although this study does not differentiate between the various possible noncancer causes of death, it indicates that cancer may be linked to other morbid conditions by either family heredity and/or family environment. (5 refs)

- 79-0550 Cancer Morbidity and Mortality Among the Insured Population of the Social Security Institute of Antioquia, Columbia.** (Eng) de Restrepo, H. E. (Instituto Colombiano de Seguro Social, Caja de Antioquia, Medellin, Columbia); Argemiro Franco, H. *Int J Epidemiol* 7(3): 285-291; 1978.

Information related to cancer cases diagnosed between 1968 and 1972 in Antioquia, Columbia, is reported. The crude annual incidence rates (per 100,000) for all cancers were 114.2/100,000 for men and 114.3/100,000 for women. The age-adjusted incidence rates (15 yr and over) for all cancers were 190.4 for men and 174.7 for women. The incidence of cancer in women exceeded that in men up to age 55, mainly due to the high rate of genital cancer in young women. The crude annual mortality rates from cancer were 42.6/100,000 for men and 38.0/100,000 for women. Skin, lung and stomach cancer predominated in men, and skin, cervix in situ, and breast cancer predominated in women. The high skin cancer rate presumably reflects exposure to the tropical sun. The incidence of cancer of the colon was typical of that found in Latin America. However, there was a colon/rectum ratio of 0.9 in men and 4.0 in women. (9 refs)

- 79-0551 Insect Damage, *Aspergillus flavus* Ear Mold, and Aflatoxin Contamination in South Georgia**

Corn Fields in 1977. (Eng) McMillian, W. W. (Univ. Georgia Coll. Agricultural Experimental Station., Tifton, GA, 31594); Wilson, D. M.; Widstrom, N. W. *J Environ Qual* 7(4): 564-566; 1978.

A survey of preharvest corn (*Zea mays* L.) in 31 counties in the coastal plain region of Georgia suggested that ears mold-
ed by *Aspergillus* spp. of the *Aspergillus flavus* group and ears damaged by insects were widespread in about 2 million acres of corn grown in the area. Ninety percent of the field-collected samples contained aflatoxin in excess of 20 µg/kg. Average ear damage by insects ranged from a low of 1.4 cm to a high of 8.9 cm. Highly significant correlations were found between insect damage and percentage of ears with visible *A. flavus* ear mold, between insect damage and aflatoxin contamination, and between percentage of ears with viable *A. flavus* ear mold and aflatoxin contamination. (12 refs)

- 79-0552 Mycotoxins in Food and the Variations in Tumor Incidence among Laboratory Rodents.** (Eng) Schoental, R. (Dept. Pathology, Royal Veterinary Coll., London, NW1 0TU, England). *Nutr and Cancer* 1(1): 13-14; 1978.

The variations in tumor incidence in the same animal species at various laboratories or even at the same laboratory at different times may be due to occasional contamination of the animal diet with mycotoxins, ie, the carcinogenic T-2 toxin, one of the irritant trichothecenes produced by *Fusarium* species, and/or the estrogenic compound zearalenone. The low fertility of *Praomys* noted at two laboratories might have been due to the presence of high concentrations of mold-derived estrogenic substances in the diet. Examples are given of the varied incidence of spontaneous stomach cancer in the South African rodent, *Praomys natalensis*, and of the varied incidence of a wide spectrum of tumors in BDX rats. The spontaneous tumors in rats, including those found in BDX rats, have been reported to resemble human cancers. This is not surprising in view of the possibility that similar mycotoxins may occasionally be present in human foodstuffs. Thus, some spontaneous tumors in animals and humans may have a common etiological factor; ie, mycotoxins. (21 refs)

- 79-0553 Excretion of Aflatoxin in the Urine of Normal Individuals and Patients with Liver Diseases in Ibadan (Nigeria).** (Eng) Bababunmi, E. A. (Dept. Biochemistry, Univ. Ibadan, Ibadan, Nigeria). In: *Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976*. International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(part 1), 2404 pp.; 1729-1736; 1978.

Urinary aflatoxin (AF) levels were assayed in three groups

of adult men living in Ibadan, Nigeria: (1) normal healthy individuals selected from different socioeconomic classes, (2) hospitalized patients with liver diseases (hepatitis, cirrhosis, hepatoma), and (3) hospitalized patients without liver disease. At least 9/10 persons in each group excreted aflatoxin B₁ (AFB₁). Aflatoxin M₁, a metabolite of AFB₁, was identified in the urine of all persons tested. Group 1 men excreted 0.2-0.7 mg AF/24-hr output of urine. In Group 2, there was considerable individual variation of AF excretion, but the mean value of 2.7 mg was higher than that of Group 1 by a factor of at least 40. The mean excretion of AF by Group 3 was not significantly different from that of Group 1. The fact that free AFB₁ and a hydroxylated metabolite were present in the urine of all three groups suggests that AF poisoning could be a major factor in the etiology of primary liver cancer in many African countries. (12 refs)

79-0554 Hepatitis B and Primary Hepatocellular Carcinoma in a European Population. (Eng) Tri-chopoulos, D. (Dept. Hygiene and Epidemiology, Univ. Athens Medical Sch., Athens, Greece); Gerety, R. J.; Sparros, L.; Tabor, E.; Xirouchaki, E.; Munoz, N. *Lancet* 2(8102): 1217-1219; 1978.

The prevalence of serological markers of active or past hepatitis B virus (HBV) infection was determined in 80 Greek patients with primary hepatocellular carcinoma (PHC), 160 age- and sex-matched controls, and 40 patients with metastatic liver cancer (MLC). The relative risk (RR) of the various patterns of HBV serological markers for PHC was calculated. Active HBV infection, indicated by positive tests for HBV surface antigen (HBsAg) or antibody to the virus-B core antigen (anti-HBc) without antibody to HBsAg (anti-HBs), was associated with PHC (RR 10.4) but not with MLC (RR 1.2). Patients without markers and those who had recovered from virus infection B (anti-HBs-positive) had the same low risk for PHC (RR 0.8). Active infection was more common in PHC patients with coexisting cirrhosis than in those without cirrhosis (67% vs 26%). Thus, the relationship between active HBV and PHC seen in African and Asian populations was demonstrated in a European Caucasian population subject to different environmental and dietary factors. (26 refs)

79-0555 Link Between Hepatoma and Hepatitis B (Letter to Editor). (Eng) Peters, R. L. (Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA); Omata, M.; Ashcava, M. *Br Med J* 2(6150): 1502; 1978.

Patients with alcoholic cirrhosis and hepatocellular carcinoma (HCC) and those with nonalcoholic hepatitis B-viral cirrhosis and HCC should be studied separately, as an inverse relationship was found between racial groups with a high occurrence of HCC in alcoholic cirrhosis and racial groups with a high occurrence of HCC in hepatitis B-viral cirrhosis.

It is likely that differences in the frequency of occurrence of HCC in various geographical areas are related to differences in the incidence of chronic hepatitis B-viral disease and, perhaps, the time in life at which hepatitis B virus was acquired. (4 refs)

79-0556 Hepatocellular Carcinoma in Great Britain: Influence of Age, Sex, HBsAg Status, and Aetiology of Underlying Cirrhosis. (Eng) Johnson, P. J. (Liver Unit, King's Coll. Hosp., Medical Sch., London, England); Krasner, N.; Portmann, B.; Eddleston, A. L.; Williams, R. *Gut* 19(11): 1022-1026; 1978.

The influence of age, sex, hepatitis B surface antigen (HBsAg) status, and etiology of underlying cirrhosis on the frequency of hepatocellular carcinoma was examined in 294 patients who had died of cirrhosis. Hepatocellular carcinoma had been detected in 71/294 patients either during life or at necropsy. Patients with hemochromatosis and HBsAg-positive chronic active hepatitis (CAH) had a high incidence of tumor development (36% and 42%, respectively), whereas those with HBsAg-negative CAH and primary biliary cirrhosis had low incidences (11% and 3%, respectively). Patients with alcoholic or cryptogenic cirrhosis formed an intermediate group with respect to tumor incidence (25% and 27%, respectively). While the male:female ratio for the whole cirrhotic group was 2:1, the male:female ratio for those patients developing a tumor was 11:1. The groups with the highest percentage of men (hemochromatosis and antigen-positive CAH groups) had the highest frequency of tumor development. The influence of HBsAg was largely accounted for by the known predisposition of males to carry HBsAg. Age was the only other significant factor, malignant change occurring more commonly in those > 50 yr old than those < 50 yr old (30% and 7% respectively). In a group of 25 patients who had developed hepatocellular carcinoma without cirrhosis, the age distribution was younger and bimodal, and the male:female ratio was 1.1:1. Of 12 women patients in this group, four had taken oral contraceptives. There appeared to be a high incidence of cancer in the families of patients without cirrhosis, which may suggest an underlying genetic factor. (27 refs)

79-0557 Thyroid Cancer in Connecticut, 1935-1975; The Changing Distribution of Histologic Types over Time (Meeting Abstract). (Eng) Mendelsohn, L. S. (Environmental Epidemiology Branch, NCI, Bethesda, MD, 20014); Meigs, J. W. *Am J Epidemiol* 108(3): 233; 1978. (no refs)

79-0558 Malignant Lymphoma Occurring in Kagoshima Prefecture, Japan: Pathological and Descriptive Epidemiological Survey Based on 849 Biopsy Materials. (Eng) Tokunaga, M. (Second Dept. Pathology, Faculty

Medicine, Kagoshima Univ., 1208-1 Usuki-cho, Kagoshima 890, Japan); Sato, E.; Tanaka, S.; Sakai, N. *Gann* 69(5): 673-678; 1978.

An epidemiological and pathological analysis was made of 849 cases of malignant lymphoma (ML) that occurred in Kagoshima Prefecture, Japan, between 1965 and 1976. The age-adjusted incidence was 3.02/100,000 (4.40 for males and 2.15 for females) over the entire study period. The av annual age-adjusted incidence per 100,000 for each 4-yr subperiod was 1.97 for 1965-1968, 2.65 for 1969-1972, and 3.38 for 1973-1976. The incidence also increased steadily with age, but the male/female ratio of 1.67 remained relatively constant. Nodal lymphomas were found in 604/789 usable tissue specimens, and they consisted of 56 Hodgkin's disease, 428 diffuse lymphomas, and 120 nodular lymphomas. Extranodal lymphomas were noted in 185 cases, and they included 67 cutaneous, 46 gastrointestinal, and 34 nasopharyngeal lymphomas, and 38 extranodal lymphomas at other sites. It is suggested that special immunogenetic or etiological factors provoke T-cell malignancy in the people of this area, resulting in the high incidence of diffuse nodal lymphoma and cutaneous extranodal lymphoma. (19 refs)

79-0559 Childhood and Adult Acute Leukaemia in Johannesburg Blacks. (Eng) Kusman, B. (Dept. Ophthalmology, Univ. Florida, Gainesville, FL); Jacobson, R. J.; MacDougall, L. G. *S Afr Med J* 54(24): 1007-1010; 1978.

The diagnosis, treatment, and follow-up of 34 black patients with acute leukemia seen at two Johannesburg hospitals during 1973-75 are discussed. Among 14 children (8 male), there were 6 cases of acute lymphoblastic leukemia (ALL), 5 of acute myeloblastic leukemia (AML), and 1 case each of monocytic, progranulocytic, and undifferentiated stem cell leukemia. Among the 20 adults (11 male), there were 12 cases of AML, 4 cases of ALL, 2 of acute monocytic leukemia, and 1 each of acute undifferentiated stem-cell leukemia and acute erythroleukemia. Common presenting symptoms of children were severe anemia, joint and bone pain, fever and/or infection, and bleeding. The most prevalent adult symptoms included bleeding manifestations, hepatomegaly, lymphadenopathy, anemia, and generalized pain. Remission was achieved in AML by the iv administration of daunorubicin (1.5 mg/kg) and cytosine arabinoside (1.0 mg/kg) every 12 hr. ALL was treated with vincristine (2 mg/m² iv/wk) and prednisone (40 mg/m² po for 3 wk); if remission did not occur, daunorubicin was added at 1.5 mg/kg/wt. Remission was initially achieved in 9/10 patients with ALL; at 36 mo, 2 children are known to be surviving in remission. Less favorably, 12/17 patients with AML achieved at least partial remission, and 3 adults are known to be alive at 10-18 mo. The emergence of acute leukemia in the young of this population conforms to the pattern seen in western countries, although a larger population of the cases were myelomonocytic than is usually seen in the western countries. (17 refs)

79-0560 BCG Vaccination and Leukemia. Epidemiological Investigations of the Influence of BCG Vaccination on Leukemia. (Ger) Ambrosch, F. (Institut für Spezifische Prophylaxe und Tropenmedizin, Kinderspitalgasse 15, A-1095 Vienna, Austria); Wiedermann, G.; Krepler, P.; Kundi, M. *Fortschr Med* 96(44): 2231-2242; 1978.

The rate of BCG vaccination of newborns and leukemia mortality during 1964-1975 in Austria were studied. After elimination of the mortality-reducing effect of improved therapy, a significant inverse correlation was found between the BCG vaccination rate and leukemia mortality in the age group 0-5 yr. From this correlation, a protection rate of 0.77 was calculated. The findings indicate the existence of a highly probable protective effect of BCG vaccination against leukemia. It will be necessary to study the relationship between BCG vaccination rate and leukemia incidence to verify this protective effect. (30 refs)

79-0561 Characteristics of Mothers at High Risk of Leukemia Developing in Their Children. (Eng) McCrea Curnen, M. G. (Div. Epidemiology, Columbia Univ. Sch. Public Health, New York, NY); Turgeon, L.; Flannery, J. T.; Varma, A. A. In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 991-997; 1977.

The possible relationship between maternal age and birth order and childhood leukemia was investigated in a cross-sectional study of 389 children with leukemia between 1946 and 1964 and in a maternal birth cohort study of 500 children. In both studies, leukemia rates were higher in children born of mothers <20 yr old (Group A) than in those born of mothers ≥20 yr old (Group B). In the cross-sectional study, the rate of 74/100,000 live births in Group A mothers obtained in the first period of the study (1946-1954) was significantly higher than that in the older mothers (p < 0.02). The incidence of leukemia was unaffected by birth order in either period. Although in the cohort analysis, leukemia rates by year of birth of the mother and by age group at delivery were also higher for Group A mothers, this finding did not carry over when women of the same cohort delivered at older ages. The follow-up is still incomplete, however, so a cohort phenomenon cannot as yet be definitely excluded. The finding that Group A mothers are more at risk than older mothers to bear a child who will develop leukemia is compatible with the hypothesis that these very young mothers are also most likely to be susceptible to infectious agents. (4 refs)

79-0562 Incidence of Leukaemia and Allied Disorders in Western Australian World War II Ex-Servicemen. (Eng) Davies, I. H. (1 Kanimbla Road, Nedlands, West-

ern Australia 6009, Australia). *Med J Aust* 2(7): 321-322; 1978.

A survey of the Leukemia Registry of the Cancer Council of Western Australia revealed an increased incidence (during 1960-1969) of leukemia and allied disorders among World War II veterans with overseas and tropical area service (OTAS), compared with those who served only in temperate Australia (2.7/1,000 vs 1.05/1,000). Specifically, OTAS was associated with an excess of lymphosarcoma, Hodgkin's disease, follicular lymphoma, multiple myeloma, polycythemia vera, acute myeloid leukemia, and acute and chronic lymphatic leukemia. Possible etiologic factors in the increased incidence are considered to be malaria, drugs (ie, mepacrine), and nitrates or nitrites in canned food. (9 refs)

79-0563 Radon Daughter Cancer in Man: Factors in Exposure-Response Relationships (Meeting Abstract). (Eng) Archer, V. E. (Div. Surveillance, Hazard Evaluation, and Field Studies, Natl. Inst. Occupational Safety and Health, Rm. 433, 350 S. Main, Salt Lake City, UT, 84101); Radford, E. P.; Axelson, O. *Health Phys* 35(6): 916-917; 1978. (no refs)

79-0564 An Evaluation of the Effect of Natural Background Radiation on Cancer Incidence (Meeting Abstract). (Eng) Cohen, J. J. (Lawrence Livermore Lab., P.O. Box 808, Livermore, CA, 94550). *Health Phys* 35(6): 916; 1978. (no refs)

79-0565 Leukemia Mortality in an Area with High Atomic Bomb Fallout (Meeting Abstract). (Eng) Lyon, J. (Univ. Utah, Salt Lake City, UT, 84132); Klauber, M.; West, D. *Am J Epidemiol* 108(3): 233; 1978. (no refs)

79-0566 Background Radiation Dose and Leukemia Mortality in North Japan. (Jpn) Sakka, M. (Tohoku Univ. Sch. Medicine, Tohoku, Japan). *Nippon Acta Radiol* 38(7): 702-706; 1978.

The relation of natural background radiation dose rate and leukemia death rate was examined in seven prefectures in north Japan, a region in which the natural environment as well as socioeconomic status are similar for all inhabitants. In the last 10 yr, more than 2,500 leukemia deaths were recorded, which were normally distributed throughout the entire area with a mean of 3.68 and a standard deviation (SD) of 1.14 deaths/10⁵ population/yr. There were no significant differences in the observed values of each prefecture in spite of the varied composition of the population. Natural background radiation dose rate had a normal distribution with a

mean of 8.98 μ R/hr and a SD of 2.12. The highest radiation dose rate in Niigata (10.44 μ R/hr) was significantly higher than the lowest in Aomori (6.48 μ R/hr) even through the leukemia death rates did not differ between these prefectures. The null hypothesis that a positive regression exists between dose rate and death rate even in the smallest dose range was not supported by this study. The leukemogenic effect of background radiation, if any, appears to be within a practical threshold. (23 refs)

79-0567 Temporal Distribution of Risk after Exposure. (Eng) Land, C. E. (NCI, Bethesda, MD, 20014); McGregor, D. H. In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 831-843; 1977.

To investigate the latency of leukemia, lung cancer, and breast cancer among Japanese A-bomb survivors, the distributions of deaths and incident cases over time were compared between low-exposure (nonexposed and exposed with 0-9 rads) and high-exposure (100+ rads) groups by age at the time of the bomb (ATB). Results confirmed previous data that had shown leukemia to have a significantly shorter latency period in heavily exposed individuals compared with lightly exposed individuals who were < 50 yr ATB but not for those \geq yr ATB. Both low-dose and high-dose lung-cancer deaths occurred in substantial numbers only among those aged over 34 yr ATB. No breast cancer cases were found among those exposed to A-bomb radiation before age 10 yr, but extremely high rates were found in the high-dose group for the 10-19 yr and 20-34 yr ATB cohorts. Although lung cancer mortality and breast cancer incidence were higher in heavily exposed compared with lightly exposed individuals, latency periods for these were similar in both groups. Taken together, this evidence implies a difference in the causation of these malignancies: leukemias may have been solely the result of A-bomb radiation, while lung and breast cancer may have been the result of radiation followed by other, age-related exposures. (14 refs)

79-0568 Cancer Mortality and Incidence in Males in Los Alamos County, New Mexico (Meeting Abstract). (Eng) Voelz, G. L. (MS-404, Health Div., Los Alamos Scientific Lab., Los Alamos, NM, 87545); Stebbings, J. H.; Haxton, L. K. *Health Phys* 35(6): 916; 1978. (no refs)

79-0569 Descriptive Epidemiology of Cancer of the Larynx in the Province of Torino, Italy. (Eng) Terracini, B. (Istituto di Anatomia e Istologia Patologica, Via

Santena 7, 10126 Turin, Italy); Anglesio, E.; Panero, M.; Vineis, P. *Tumori* 64(5): 445-456; 1978.

The geographical distribution of laryngeal cancer was studied in the province of Torino between 1965 and 1969, and its possible correlation with certain environmental factors was investigated. The age-standardized incidence rate of laryngeal cancer in men was 14.7/100,000/yr in the city of Torino and 8.4/100,000/yr in the remainder of the province. These rates are among the highest in Europe. To validate the methodology in the study of laryngeal cancer, the investigation was extended to bladder cancer and to cancer in children. When the 291 towns in the province were grouped according to total population number and to the extent of industrialization, no correlations were found between the incidences of bladder, laryngeal, or infantile cancer and population number. However, the incidence of laryngeal cancer in men in highly industrialized towns was 40.7/100,000/yr, while that in men living in poorly industrialized towns was only 17.9/100,000/yr. Bladder cancer was also correlated with industrialization, but cancer in children was not correlated with either population number or industrialization. (21 refs)

79-0570 Negligible Role of Alcohol and Tobacco in the Etiology of Esophageal Cancer in Iran--A Case Control Study. (Eng) Mahboubi, E. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NB); Day, N. E.; Ghadirian, P.; Salmasizadeh, S. In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp; 1149-1159; 1977.

A case-control study was conducted to determine the influence of alcohol, tobacco, and opium use on esophageal cancer (EC) in an area with a high EC incidence, the Caspian Littoral of Iran. In interviews with 151 patients and 301 healthy controls, alcohol consumption and smoking were found to be negligible. Regular opium use appeared to increase the cancer risk, but the possibility of bias in responses could not be excluded. It is suggested that the long-term nutritional deficiencies that exist in this region may be related to the increased risk of EC, without the added influence of tobacco or alcohol. These deficiencies are particularly severe among Turkomans. Since the present study failed to pinpoint any specific factor or known carcinogen, the combination and/or interaction of several factors may be involved in the etiology of EC. These factors include nutritional deficiency, trauma to esophageal mucosa through ingestion of dust and silica particles, consumption of hot beverages, and dietary constituents such as mycotoxins produced by fungi favored by environmental conditions and, possibly, extraneous carcinogenic seeds in wheat. (13 refs)

79-0571 Etiology and Epidemiology of Cancer of the Mouth and Pharynx in Switzerland. (Fre) Ju-

nod, B. (Institut universitaire de medecine speciale et preventive, Hopital Sandoz, CH-1011 Lausanne, Switzerland); Pasche, R. *Schweiz Med Wochenschr* 108(24): 882-887; 1978.

The epidemiology and etiology of cancer of the mouth and pharynx in Switzerland were studied. The incidence is 6.4/100,000, which is considerably higher than in most other industrialized countries (1.4-4.9/100,000), but significantly lower than in France (13.1/100,000). The male/female ratio is 7.4, which is comparable to that in countries with high overall incidence. Cancers of these sites mostly affect relatively young men. An etiological survey of 226 patients revealed a correlation between cigarette smoking and alcohol consumption on one hand, and the incidence of cancer of the mouth and pharynx on the other hand. Smokers smoking ≥ 10 cigarettes a day accounted for 87.9% of the 226 patients, while nonsmokers accounted for 6.8% only. Persons consuming ≥ 5 deciliters of wine daily accounted for 82% of the 226 patients. The cancer incidence was highest among smokers who were also heavy drinkers. While ethanol proper is not carcinogenic, it facilitates the penetration of carcinogenic substances through the mucosa. It seems likely that some alcoholic beverages available in Switzerland contain carcinogenic substances. The findings suggest that the beverages consumed by the cancer patients and those consumed by controls should be tested for mutagenicity. (32 refs)

79-0572 Prospective Studies on Cancer Epidemiology Based on Census Population in Japan. (Eng) Hirayama, T. (Epidemiology Div., Natl. Cancer Center Res. Inst., Tokyo, Japan). In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp; 1139-1148; 1977.

The 9-yr follow-up results of a Japanese prospective study on the health consequences of cigarette smoking and alcohol consumption are presented. Among the 265,118 adults (aged ≥ 40 yr) studied, there was a total of 24,668 deaths, 6,485 from cancer. Men and women who smoked cigarettes daily had the highest death rates from cancer, and the risk was particularly high when smoking was initiated during adolescence. Smoking significantly increased the risk of cancer of all sites, the risk of cancer of the mouth, pharynx, esophagus, stomach, liver, pancreas, larynx, and lungs in men, and the risk of cancer of the mouth, stomach, liver, larynx, and lungs in women. Daily alcohol consumption enhanced the risk of cancer of the mouth, pharynx, esophagus, liver, and lungs in men and cancer of the esophagus and lungs in women. The risk among occasional drinkers was nearly identical to that of nondrinkers. Among individuals who were both smokers and drinkers, there was an elevated risk for digestive tract cancers, including cancer of the mouth, pharynx, esophagus, and liver. The risk of laryngeal and lung cancer was enhanced by smoking, regardless of drinking habits, but the risk of

digestive tract cancers was selectively high when smoking and drinking were combined. Thus, the oncogenicity of cigarette smoking in the larynx and lung differs from that in the digestive tract. It is suggested that the former represents contact carcinogenesis and the latter metabolic carcinogenesis. (3 refs)

79-0573 Cancer Mortality Among Carpenters in Hawaii.

(Eng) Budy, A. M. (Pacific Biomedical Res. Center, Univ. Hawaii, Honolulu, Hawaii, 96822); Rashad, M. N. In: *Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976*. International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part I): 1193 pp.; 901-913; 1977.

Leukemia and lung cancer mortality in carpenters in Hawaii was compared before (1935-1969) and after (1970-1973) introduction of the use of water-soluble, copper-chrome-arsenates (arsenic acid and pentavalent arsenic compounds) as wood preservatives. Prior to 1970, FCAP (a preservative containing disodium arsenate) was used exclusively, with 1948-1951 representing the period of lowest exposure. Compared with a general population control group, the death rate among carpenters was significantly higher. Results also revealed an excess cancer death rate compared with controls, which was consistent during both usage periods (1935-1969 and 1970-1973): the relative increase in risk for cancer death in carpenters was 2.15 for the early period and 2.29 for the later period. These results are in general agreement with previous studies that showed an excess of lung cancer and leukemia-lymphoma among individuals occupationally exposed to wood. (7 refs)

79-0574 A Survey of a Population Exposed to High Concentrations of Arsenic in Well Water in Fairbanks, Alaska. (Eng) Harrington, J. M. (Center Disease Control, Atlanta, GA, 30333); Middaugh, J. P.; Morse, D. L.; Housworth, J. *Am J Epidemiol* 108(5): 377-385; 1978.

An epidemiologic study of 211 persons exposed to high arsenic concentrations (up to 10,000 $\mu\text{g/l}$) in their well water was carried out to assess exposure, absorption, and clinical sequelae of chronic arsenic ingestion. In well-water drinkers, close correlations were found between well water arsenic levels and urinary arsenic and between well water arsenic levels and hair arsenic levels. Nail arsenic levels correlated poorly with water arsenic exposure. No clinical or hematologic abnormalities were found. (23 refs)

79-0575 Asbestos-associated Disease in United States Shipyards. (Eng) Selikoff, I. J. (Environmental Sciences Lab., Mount Sinai Sch. Medicine, City Univ. New

York, New York, NY); Hammond, E. C. *CA* 28(2): 87-99; 1978.

Data are presented on asbestos-associated diseases among US, Canadian, British, and French shipyard workers. In a group of 1,117 asbestos insulation workers in the New York area, most with >20 yr exposure had abnormal x-rays and most lung cancers, including mesothelioma, occurred after 30 yr. Of 1,000 Groton, Connecticut, shipyard workers, one-half showed x-ray evidence of pulmonary or pleural changes indicative of asbestosis. Parenchymal disease was present in 36.8% and pleural changes in 29.7% of 364 workers with ≥ 20 yr exposure. The high proportion of asbestotic x-ray changes suggests an increased future risk of asbestos-associated neoplasms, which include lung cancer, pleural or peritoneal mesothelioma, and esophageal, gastric, colorectal, oropharyngeal, laryngeal, and renal cancer. Recommendations for ameliorating the hazards of asbestos exposure are outlined. (19 refs)

79-0576 Five-Year Review of Sputum Cytology in Workers at Nickel Sinter Plant (Meeting Abstract).

(Eng) McEwan, J. C. (Ontario Ministry Labour, Toronto, Ontario, Canada). *Ann Clin Lab Sci* 8(6): 503; 1978. (no refs)

79-0577 Second Study of the Incidence and Mortality of Cancer of Respiratory Organs Among Workers at a Nickel Refinery (Meeting Abstract).

(Eng) Pedersen, E. (Cancer Registry of Norway, Oslo, Norway); Andersen, A.; Hogetveit, A. *Ann Clin Lab Sci* 8(6): 503-504; 1978. (no refs)

79-0578 Lung Cancer in New Caledonia, A Nickel Smelting Island. (Eng) Lessard, R. (Sch. Public Health, Univ. Michigan, Ann Arbor, MI); Reed, D.; Maheux, B.; Lambert, J. *J Occup Med* 20(12): 815-817; 1978.

The occurrence of lung cancer in New Caledonia during 1970-1974 and its possible association with nickel refining were studied. Ninety-two cases of lung cancer were diagnosed in this period. The av annual age-adjusted incidence rate was approx seven times higher in men than in women. The total incidence rate for all men living in Noumea, the capital city and the site of the Ni smelter, was higher (53) than the rate for all rural men (34). However, there was no consistent pattern among racial groups. These incidence rates were three to six times higher than those in 5/6 other South and Central Pacific countries investigated, and they were similar to rates in industrialized countries. There was a significant inverse relationship between av annual incidence rate and distance of residence from the smelter. The association of lung cancer, smoking, and Ni occupation was analyzed in 68/81 male patients for whom this information was available. Lung cancer and Ni occupation were significantly associated independently of the effects of age and cigarette smoking [relative risk (RR), 3.0]. Lung cancer and cigarette smoking were significantly associated independently of the effects of age and Ni occupation (RR, 22). There was no significant interaction

between cigarette smoking and Ni occupation that would increase the RR of each variable separately. (16 refs)

- 79-0579 Oat Cell Lung Cancer in Selected Occupations. A Case-Control Study.** (Eng) Wegman, D. H. (Dept. Labor and Industries, Div. Occupational Hygiene, Commonwealth Massachusetts, Executive Office Manpower Affairs, 39 Boylston St., Boston, MA, 02116); Peters, J. M. *J Occup Med* 20(12): 793-796; 1978.

A case-control study was made to evaluate reported occupation in 91 men with oat cell cancer of the lung identified in the Massachusetts Tumor Registry between 1965 and 1972. The patients were matched for age at diagnosis (limit, 60 yr) and reporting hospital with 91 CNS cancer patients also obtained from the registry, and the two groups were compared with respect to occupation and smoking history, ascertained by investigation of tumor registry form, death certificate, medical record, and interview information, which was obtainable in 71% of cases plus controls. The mean age at diagnosis was 52 yr for both cases and controls. Eight cases had been transportation equipment operators vs one control, and the mean age of these cases was the lowest among all cases and was 4 yr below that of the control in this occupation (46 vs 50). Fourteen cases were classified as laborers vs only 3 controls, but a more specific investigation as to type of labor did not reveal any particular pattern. Blind reevaluation of occupation reclassified four men in transportation-related industries as transportation equipment operators, and all four were subsequently identified to be cases. Cigarette smokers comprised 94% of cases and 77% of controls for whom this information could be determined. These results are consistent with the hypothesis that an excess risk of lung cancer in transportation equipment operatives is related to chronic exposure to engine exhaust. (18 refs)

- 79-0580 Investigation of Possible Association of Exposure to Nickel and Lung Cancer Mortality in Workers at an Aircraft Engine Factory (Meeting Abstract).** (Eng) Bernacki, E. J. (United Technologies, Inc., Hartford, CT); Parsons, G. E.; Sunderman, F. W. *Ann Clin Lab Sci* 8(6): 504; 1978. (no refs)

- 79-0581 Iatrogenic Carcinoma Induction by the Use of Tar Preparations in Dermatology.** (Ger) Gotz, H. (Dermatologische Klinik und Poliklinik, Universitat Essen, Hufelandstr. 55, 4300 Essen, W. Germany); Deichmann, B.; Zabel, M. *Z Hautkr* 53(21): 751-755; 1978.

Questionnaire replies obtained from 1,075 dermatologists in West Germany concerning the possible carcinogenic effect of dermatological tar and tar preparations are evaluated. Seventeen dermatologists observed precancerous lesions and one observed carcinoma in connection with the use of tar preparations, regardless of the exposure of the treated skin surface to UV light. Two of these 18 dermatologists gave no further

details, while 10 indicated occupational exposure to tar, and 2 reported precancerous lesions following treatment with tar preparations and arsenic. Only four dermatologists believed the precancerous lesions and carcinoma to have been caused by the use of dermatological tar preparations. The carcinoma or precancerous lesions that develop following long-term treatment of chronic dermatoses with tar preparations, arsenic, x-rays, and exposure to UV light is an additive effect, in which it is impossible to determine contribution of the different etiological factors. (14 refs)

- 79-0582 40 Year Epidemiologic Evaluation of Salivary Neoplasia in Rochester, Minnesota (Meeting Abstract).** (Eng) Bouquot, J. (West Virginia Univ., Morgantown, WV, 26506); Lovested, S.; Weiland, L.; Kurland, L. *J Dent Res* 58(Special Issue A): 419; 1979. (no refs)

- 79-0583 The Use of Logistic Regression for Modelling Risk Factors: With Application to Non-melanoma Skin Cancer.** (Eng) Vitaliano, P. P. (Sch. Medicine, Univ. Washington, Seattle, WA, 98195). *Am J Epidemiol* 108(5): 402-414; 1978.

Logistic regression was used to estimate the relative risk of basal and squamous skin cancer for factors such as cumulative lifetime solar exposure, age, complexion, and "tannability". In contrast to previous studies, a subject's exposure to the sun was determined by interview data in this study, rather than by indirect means such as latitude or by the number of sun days in the subject's environment. A relatively new technique was used to estimate relative risk by controlling for confounding and testing for effect modification. A linear effect for the relative risk of cancer versus exposure was found. Tannability was shown to be a more important risk factor than complexion. This result is consistent with results obtained by a previous investigator. (22 refs)

See also:

- *(Rev.): 79-0003, 79-0015, 79-0024, 79-0026, 79-0029, 79-0030, 79-0034, 79-0035, 79-0039, 79-0042, 79-0045, 79-0052, 79-0054, 79-0056, 79-0057, 79-0059, 79-0069, 79-0079, 79-0086, 79-0088, 79-0089, 79-0090, 79-0091, 79-0092, 79-0094.
*(Chem.): 79-0104, 79-0105, 79-0106, 79-0111, 79-0142, 79-0145, 79-0162, 79-0179, 79-0229, 79-0246, 79-0247, 79-0295, 79-0296, 79-0311, 79-0312, 79-0314, 79-0316, 79-0318, 79-0319.
*(Phys.): 79-0321, 79-0323, 79-0324, 79-0327, 79-0333, 79-0346, 79-0348, 79-0353, 79-0354, 79-0359, 79-0361, 79-0365, 79-0368.
*(Viral): 79-0438.
*(Immun.): 79-0477, 79-0478, 79-0481.
*(Path.): 79-0519, 79-0528.

MISCELLANEOUS

79-0584 The Resolution of Membrane Proteins Based Upon Size, Charge, and Hydrophobicity. (Eng)

Fernandes, P. B. (Dept. Microbiology and Immunology, Temple Univ., Sch. Medicine, 3400 N. Broad St., Philadelphia, PA, 19140); Nardi, R. V.; Franklin, S. G. *Anal Biochem* 91(1): 101-114; 1978.

Membrane proteins from several strains of *Escherichia coli*, *Salmonella enteritidis*, and *Proteus mirabilis* were resolved with a polyacrylamide gel electrophoresis system based on the addition of the nonionic detergent Triton X-100 to acetic acid-urea polyacrylamide gels. The system allows the detection of microheterogeneity in histones involving the substitution of neutral residues, and it separates proteins on the basis of charge, size, and hydrophobicity. The optimal resolution conditions of 12 mM Triton and 8 M urea were determined by electrophoresis through transverse urea and Triton X-100 gradients. The system was successful not only in distinguishing different genera of gram-negative bacteria, but also in analyzing type and strain differences. A two dimensional method using Triton-urea-acetic acid gels in the first dimension and sodium dodecyl sulfate gels containing 15% acrylamide in the second dimension was able to resolve proteins that could not be conveniently resolved by either method individually. This system appears to provide a promising means for analyzing membrane envelope proteins that are due to missense mutations. (39 refs)

79-0585 Changes in Intramembranous Particle Topography and Concanavalin A Receptor Mobility Associated with Myoblast Differentiation. (Eng) Furcht, L. T.

(Dept. Lab. Medicine and Pathology, Univ. Minnesota, Medical Sch., Box 609 Mayo, Minneapolis, MN, 55455); Wendelschafer-Crabb, G. *Differentiation* 12(1): 39-45; 1978.

Two parameters of cell surface organization accompanying myoblast differentiation, ie, plasma membrane intramembranous particle (PMP) distribution and concanavalin A (con-A) receptor topography and redistribution, were examined by freeze-fracture techniques and by ultrastructural cytochemistry of L6 myoblasts, respectively. Undifferentiated mononucleated cells were seen to have a clustered distribution of PMP on the majority of the fracture faces. A more uniform PMP distribution was associated with cell differentiation and cell fusion. In undifferentiated or differentiated, glutaraldehyde-fixed cells reacted with con-A, a uniform con-A distribution was observed on the cell surfaces. In contrast, over 99% of unfixed, live, differentiated cells showed

a profound redistribution of the lectin, while receptors remained in a uniform array on 95% of the live, undifferentiated cells. In addition to the membrane binding, con-A was observed to bind to an extracellular filamentous matrix seen in high-density, undifferentiated cultures, which then appeared to be degraded with differentiation and myoblast fusion. These studies show that a number of membrane changes, both structural and dynamic, occur with myoblast differentiation. (28 refs)

79-0586 Transport of DNA from Lymphocytes to Fibroblasts in Culture. (Eng) Harris, G. (Div. Experimental Pathology, Kennedy Inst. Rheumatology, Bute Gardens, London W6 7DW, England); Olsen, I.; Furner, P.

Differentiation 12(1): 1-13; 1978.

The transfer of radioactivity from labeled DNA of CBA mouse spleen lymphocytes to recipient hamster lung V79 fibroblasts was investigated. Lymphocytes were stimulated with 4 µg/ml Concanavalin A and incubated with (³H)-thymidine (2 µCi/ml, 5 µM), after which time 2 x 10⁶ of the labeled cells were added to 2 x 10⁵ fibroblasts. When added to V79 cells in logarithmic growth phase, autoradiography showed that all fibroblasts were labeled within 2 hr, and that > 50% of total radioactivity moved from donor to recipient cell nuclei in 6 hr. Although the rate of incorporation in confluent fibroblast cultures was slower, all these cells were labeled within 24 hr. When the labeled donor DNA, substituted with bromodeoxyuridine, was followed in recipient cells by buoyant density measurements in cesium chloride gradients, it associated with the nuclear DNA of the host fibroblasts. The donor DNA was not only broken down and its products reutilized for fresh DNA synthesis in the recipient cell, but relatively intact lymphocyte DNA was also incorporated. This intact DNA was retained in confluent recipient cell cultures for much longer periods than in actively growing fibroblast cultures. These results show that lymphocytes can be a source of macromolecular DNA for other cells, perhaps for transport of regulatory or informational molecules. (29 refs)

79-0587 Tertiary Structural Collapse of DNA in 5.5 M LiCl Inferred from Quasielastic Light Scattering (Meeting Abstract). (Eng) Parthasarathy, N. (Dept. Chemistry, Univ. Missouri-Kansas City, Kansas City, MO);

Schmitz, K. S.; Cowman, M. *Biophys J* 25(2, part 2): 221a; 1979. (no refs)

79-0588 Molecular Heterogeneity of DNA Polymerase α from P815 Mouse Mastocytoma Cells. (Eng) Bieri-Bonniot, F. (Pharmaceuticals Div., CIBA-Geigy Ltd., Basel, Switzerland); Schuerch, A. R. *FEBS Lett* 96(1): 192-196; 1978.

Data on the separation and partial analysis of two forms of DNA polymerase α from P815 mouse mastocytoma cells are presented, the two peaks of activity being distinguished by their affinity for poly(dT) on poly(dT)-CL-Sepharose columns. Both forms exhibited properties characteristic of DNA polymerases α (sensitivity to N-ethylmaleimide, dependency on dithiothreitol, molecular size range), but they differed in their relative ability to copy various synthetic templates, in the ionic conditions necessary to their max activity, and in the degree to which they are protected against heat inactivation by 5 mM dithiothreitol. One form migrated slightly faster than the other on glycerol gradients, possibly due to a difference in configuration or quaternary structure. It is concluded that there are differences in the molecular structure and properties of the two forms. (15 refs)

79-0589 Photoaffinity Labeling of the Ribosomal Peptidyl Transferase Site with Synthetic Puromycin Analogues. (Eng) Vince, R. (Dept. Medical Chemistry, Coll. Pharmacy, Univ. Minnesota, Minneapolis, MN, 55455); Brownell, J.; Fong, K. L. *Biochemistry* 17(25): 5489-5493; 1978.

The puromycin analog N ϵ -(2-nitro-4-azidophenyl)-L-lysiny puromycin aminonucleoside (NAP-Lys-Pan) was studied for its potential as a photoaffinity label in the peptidyl transferase center of 70S ribosomes. The analog was synthesized by a condensation reaction of N ϵ -tert-butyloxycarbonyllysine and 4-fluoro-2-nitrophenylazide, with coupling of the product to puromycin aminonucleoside followed by deblocking. The analog demonstrated excellent acceptor activity in the peptidyl transferase reaction, exhibiting an affinity for the acceptor (A) site (as indicated by Michaelis constants) only slightly lower than that of puromycin. Furthermore, its aryl azide group was capable of being decomposed by visible light. This photosensitivity was employed to link the analog covalently to *Escherichia coli* ribosomes, followed by a polyuridine direction of N-acetyl[14 C]-L-phenylalanyl-tRNA (Ac(14 C)-Phe-tRNA) to the peptidyl sites of the ribosomes. Subsequently, transpeptidation transferred Ac(14 C)Phe to the NAP-Lys-Pan in the A site with a labeling efficiency of 2.6%. When the ribosomes were dissociated into subunits by dialysis, scintillation counting indicated that the radioactivity was concentrated in the 50S subunit, in which the peptidyl

transferase center is located, confirming the specificity of labeling. (13 refs)

79-0590 γ -Glutamyl Transpeptidase and Malignant Transformation of Cultured Liver Cells. (Eng) Huberman, E. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Montesano, R.; Drevon, C.; Kuroki, T.; St. Vincent, L.; Pugh, T. D.; Goldfarb, S. *Cancer Res* 39(1): 269-272; 1979.

The relationship between γ -glutamyl transpeptidase (GGT) and malignant cell transformation was analyzed in malignant and nonmalignant cultured epithelial cell lines derived from rat livers and fibroblastic cell lines derived from hamsters and mice. GGT activity was prominent (25% to 90% of cells) in 3/5 malignant epithelial liver cell lines. None of the nine fibroblastic or four nonmalignant epithelial cell lines exhibited GGT activity. These results suggest that by use of GGT activity, a significant fraction of spontaneously or chemically induced malignant cells can be detected in cultured liver cells. Thus, in conjunction with other markers, this marker may help in identifying tumorigenic cells in liver epithelial cultures. (30 refs)

79-0591 Ultrastructure of Elementary Chromatin Particles Studied by Surface-Spreading Whole-Mount Electron Microscopy. (I) Condensation of Elementary Chromatin Particles in Synchronized L5178Y Cells (Meeting Abstract). (Eng) Watanabe, M. (Tokyo Metropolitan Isotope Res. Inst., Tokyo, Japan); Kinjo, Y. *J Electron Microscop* (Tokyo) 27(4): 380; 1978. (no refs)

79-0592 Inhibition of Growth of Transformed Cells and Tumors by an Endogenous Acceptor of Galactosyltransferase. (Eng) Podolsky, D. K. (Gastrointestinal Unit, Massachusetts General Hosp., Boston, MA, 02114); Weiser, M. M.; Isselbacher, K. J. *Proc Natl Acad Sci USA* 75(9): 4426-4430; 1978.

Investigation was made of the effect of a cancer-associated galactosyltransferase acceptor (CAGA), a glycopeptide purified from human malignant effusions, on cell growth in vitro and in vivo. CAGA (0.5-1.5 μ g/ml, 2 ml/dish) was added to cultures of normal and polyoma virus-transformed baby hamster kidney and NIL cells (BHK, NIL, BHKpy, and NILpy, respectively), human breast adenocarcinoma cells (BT-20), human pancreatic carcinoma cells, and Chang cells at the time of plating. CAGA inhibited attachment and growth of the transformed cells significantly but had minimal effects on nontransformed cells. Transformed hamster and

human malignant cells appeared more rounded and possessed both vacuolar and refractile inclusions and they were killed by as little as 0.5 $\mu\text{g/ml}$ CAGA, but nontransformed cells did not show a significant change in growth or morphology. Inoculation of hamsters with CAGA (20 μg sc or ip) at the time of their inoculation with BHKpy or BHKpygiv inhibited tumor growth 69%-94% by the sc route and 39%-67% by the ip route. Administration of CAGA after the development of a palpable tumor (approx 0.5 cm) reduced the growth rate 60%-85% and, in some cases, markedly reduced tumor wt and caused tumors to disappear. Thus, CAGA inhibits tumor growth in vitro and in vivo, but the mechanism of inhibition remains to be determined. (28 refs)

79-0593 Morphological Studies of 5-Bromodeoxyuridine-treated Murine Melanoma Cells In Vivo (Meeting Abstract). (Eng) Gyi, K. K. (Dept. Anatomy, Georgetown Univ., Washington, DC); Wrathall, J. R. *J Cell Biol* 79(2, part 2): 71a; 1978. (no refs)

79-0594 Biological Effects of Intercellular LETS Glycoprotein Matrices (Meeting Abstract). (Eng) Chen, L. B. (Sidney Farber Cancer Inst., Harvard Medical Sch., Boston, MA, 02115); Murray, A.; Segal, R. S.; Walsh, M. L. *J Cell Biol* 79(2, part 2): 157a; 1978. (no refs)

79-0595 Association Between Cell Surface Fibronectin (LETS Protein), Anchorage Independence and Tumorigenicity in Animal Cells (Meeting Abstract). (Eng) Canary, P. K. (Dept. Genetics, Albert Einstein Coll. Medicine, Bronx, NY); Jackson, M. J.; Shin, S. *J Cell Biol* 79(2, part 2): 397a; 1978. (no refs)

79-0596 Transformation is an Alternative to Normal Muscle Development (Meeting Abstract). (Eng) Kaufman, S. J. (Dept. Microbiology and Sch. Basic Medical Sciences, Univ. Illinois, Urbana, IL, 61801). *J Cell Biol* 79(2, part 2): 23a; 1978. (no refs)

79-0597 Direct Resorption of Bone by Human Breast Cancer Cells In Vitro. (Eng) Eilon, G. (Dept. Medicine, Div. Endocrinology and Metabolism, Univ. Connecticut Health Center, Farmington, CT, 06032); Mundy, G. R. *Nature* 276(5689): 726-728; 1978.

The process by which human breast cancer cells resorb bone

was investigated in vitro. In three separate experiments, supernatants from cultures of the human breast cancer cell line MCF-7 caused the release of previously incorporated ^{45}Ca from live and dead fetal rat long bones. Similar results were obtained when the bones were cocultured with the MCF-7 cells. The bone matrix was also resorbed by the cells and their conditioned media. Supernatants from four other established breast cancer cell lines also caused mineral release from devitalized fetal rat bones, whereas other normal and neoplastic cells had no effect. The effects of MCF-7 cells on bone could not be ascribed to changes in pH. Bones cultured with prostaglandin E_2 (10^{-6} M) showed many giant multinucleated osteoclasts, whereas bones cultured with supernatants from the MCF-7 cultures showed no detectable osteoclasts. However, the increase in ^{45}Ca release observed in bones cultured with prostaglandin and those cultured with the cancer cells was similar (80% and 83% more than corresponding controls, respectively). Studies in which live bones were cultured with cortisol and phosphate, both of which inhibit the effects of osteoclasts on bone, confirmed that osteoclasts are not required for breast cancer cells to resorb bone. That bone resorption stimulated by MCF-7 cells occurs independently of prostaglandins was confirmed by culturing MCF-7 cells with indomethacin (10^{-5} M) on live bones; indomethacin had no effect on ^{45}Ca release. The results demonstrate that some cultured human breast cancer cells can resorb bone directly in vitro, independently of osteoclast stimulation. (20 refs)

79-0598 Totipotent Cells of Parthenogenetic Origin in a Chimaeric Mouse. (Eng) Stevens, L. C. (Jackson Lab., Bar Harbor, ME, 04609). *Nature* 276(5685): 266-267; 1978.

Evidence is given that early embryonic parthenogenetic (PG) mouse cells are totipotent: they can give rise to fully functional ova that, when fertilized by sperm, develop into normal individuals. PG four- and eight-cell embryos of the pigmented mouse strains LT/Sv and LTXBJ and their F_1 hybrids and embryos from normally fertilized eggs of albino strain 129/Sv and (129 x A/He) F_1 were flushed from the oviducts of superovulated females. The zona pellucida was removed, one normal and two PG embryos were aggregated, and 456 aggregated triplets were transferred to the uteri of 47 pseudopregnant (SJL x C57BL/10) F_1 females. Twenty-four offspring were produced, 6 (4 males, 2 females) of which were identified as chimeras by their partially pigmented coats and irises. All were mated with strain 129 mice. The four males sired 285 offspring, all albinos. One female produced 33 albino offspring, the other five litters of 29 albino offspring. Her sixth and last litter contained two albino and two pigmented offspring. The latter could only have been derived from ova of PG origin (LT) fertilized by normal albino (129) sperm. Increasing the number of cells in a PG embryo prolonged its survival in utero. Even though pure PG embryos will not survive in utero, these results demonstrate that their cells are capable of participating in normal development when as-

sociated with normal cells. The production of offspring with the *C* and *Hbb-s* (*s* = single) alleles from an aggregation chimera between a PG *C/C Hbb-s/Hbb-s* and a normal *c/c Hbb-d/Hbb-d* (*d* = diffuse) embryo demonstrates that fully functional totipotent ova of PG origin were produced. (12 refs)

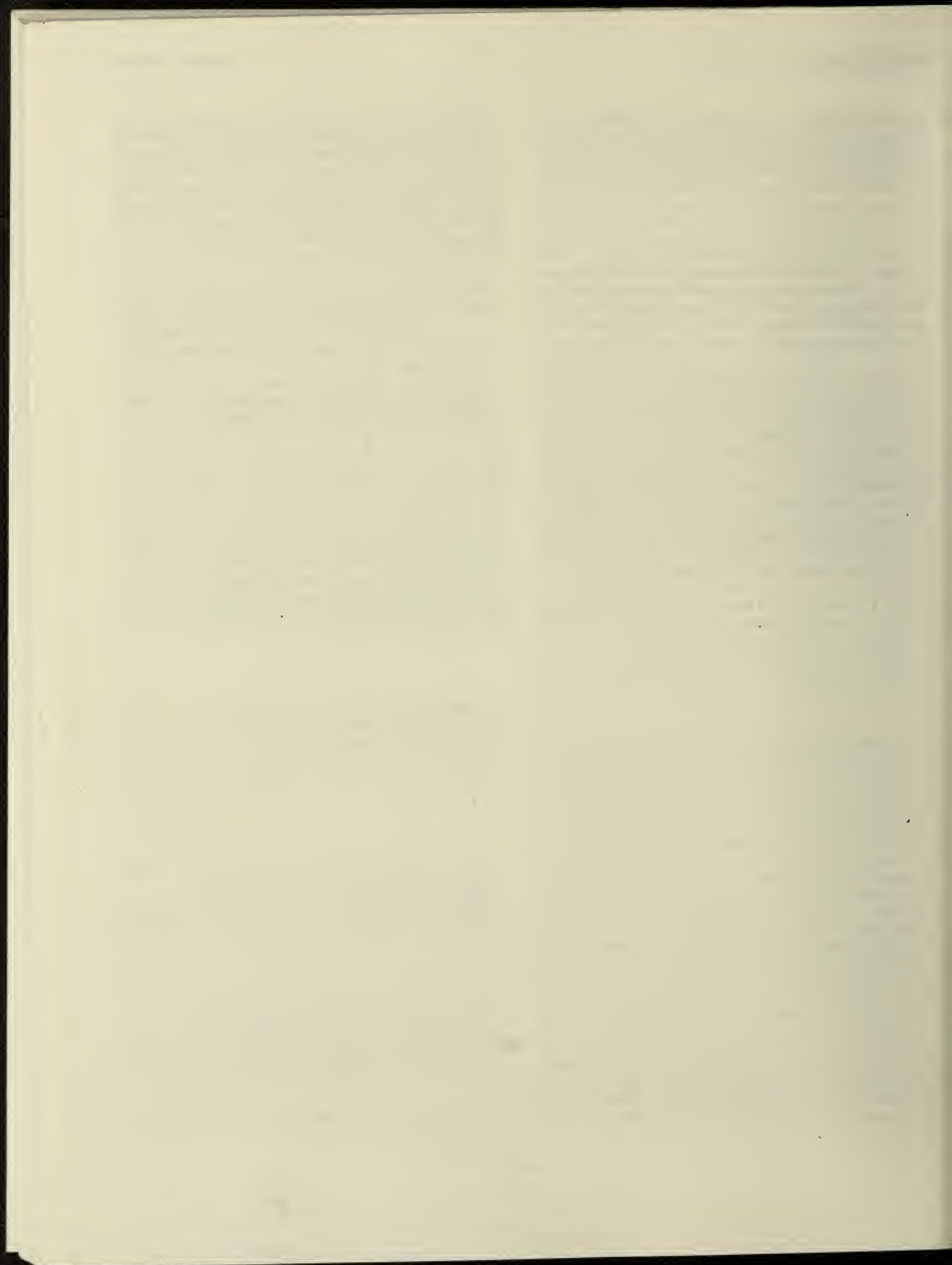
79-0599 Use of the Beta-Binomial Distribution in Dominant-Lethal Testing for "Weak Mutagenic Activity". (Eng) Vuataz, L. (Mathematics Section, Nestle Products Technical Assistance Co. Ltd., CH1814 La Tour de Peilz, Switzerland); Sotek, J. *Mutat Res* 52(2): 211-230; 1978.

Computer simulations of dominant-lethal test experiments were performed to compare the behavior of the beta-binomial test with that of the traditional chi-square test on 2 x 2 frequency tables and to estimate the type I error rate. Three models were used: (1) the mating ratio is 1, and the probability (*p*) that an implant will die is distributed over the couples, (2) the mating ratio is > 1, and *p* is distributed over the males, the females mated to the same male being binomial observations of the value of *p* supplied by the male, and (3) the mating ratio is > 1, and *p* is distributed over the females. The av rates of dead implants for the treatment and control groups were 0.10 and 0.08, respectively, and significance level was 0.05. Although the chi-square test was applicable when *p* was constant in a group, the type I error rate increased from 0.05 to 0.30 when *p* was distributed over experimental units. The

beta-binomial simulation results, however, indicated an excellent overall fit of the model in each of the experimental groups. Av powers of 0.72 and 0.85 were reached for groups of 300 and 450 animals, respectively, when the increment in the rate of dead implants was 2%. It is recommended that for a given number of animals/group, a mating ratio larger than one should be used, and the males should be the considered experimental units. (8 refs)

79-0600 Ectopic Production of High Molecular Weight Calcitonin and Corticotropin by Human Small Cell Carcinoma Cells in Tissue Culture: Evidence for Separate Precursors. (Eng) Bertagna, X. Y. (Dept. Medicine, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232); Nicholson, W. E.; Pettengill, O. S.; Sorenson, G. D.; Mount, C. D.; Orth, D. N. *J Clin Endocrinol Metab* 47(6): 1390-1393; 1978.

The presence of immunoreactive-calcitonin (IR-CT) in the ACTH-secreting DMS-79 continuous line of human small cell lung carcinoma cells was demonstrated. Two major and one minor high-mol wt forms of IR-CT were observed after gel exclusion chromatography under denaturing conditions. None of these IR-CT materials was extracted from DMS-79 medium by affinity chromatography using an ACTH antibody covalently bound to agarose. The results did not support the existence of a common CT/ACTH/ β -lipotropin/ β -endorphin precursor molecule. (13 refs)



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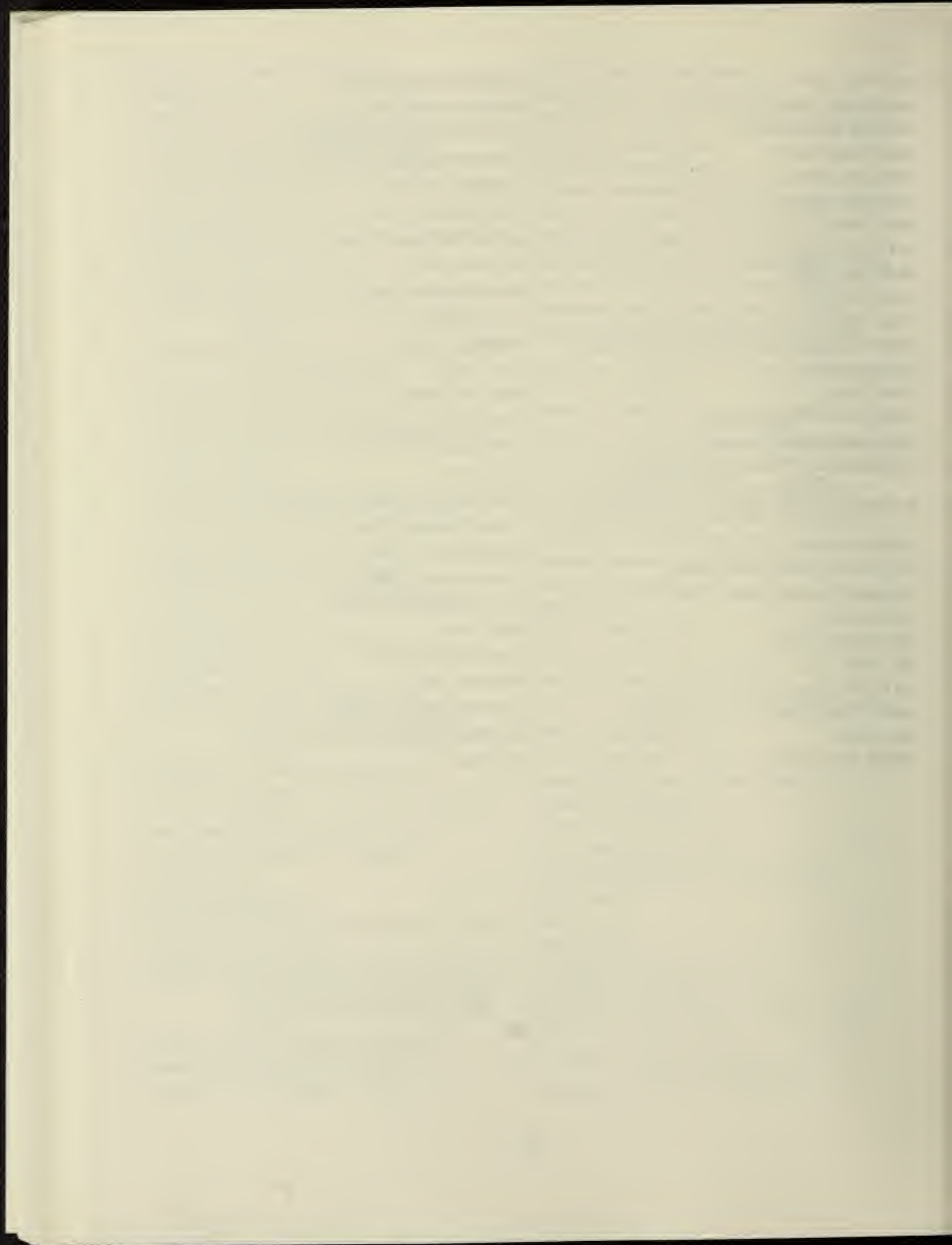
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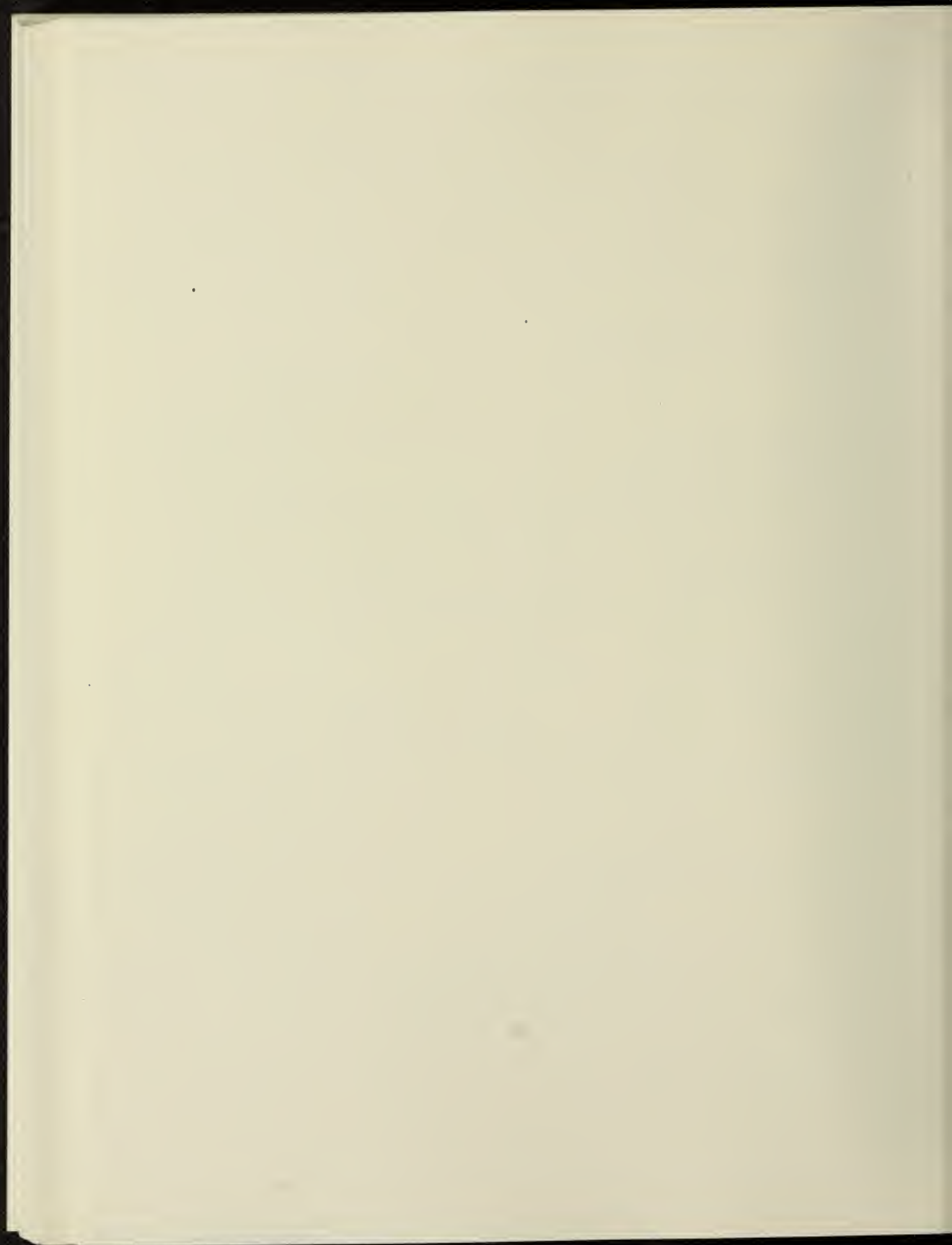
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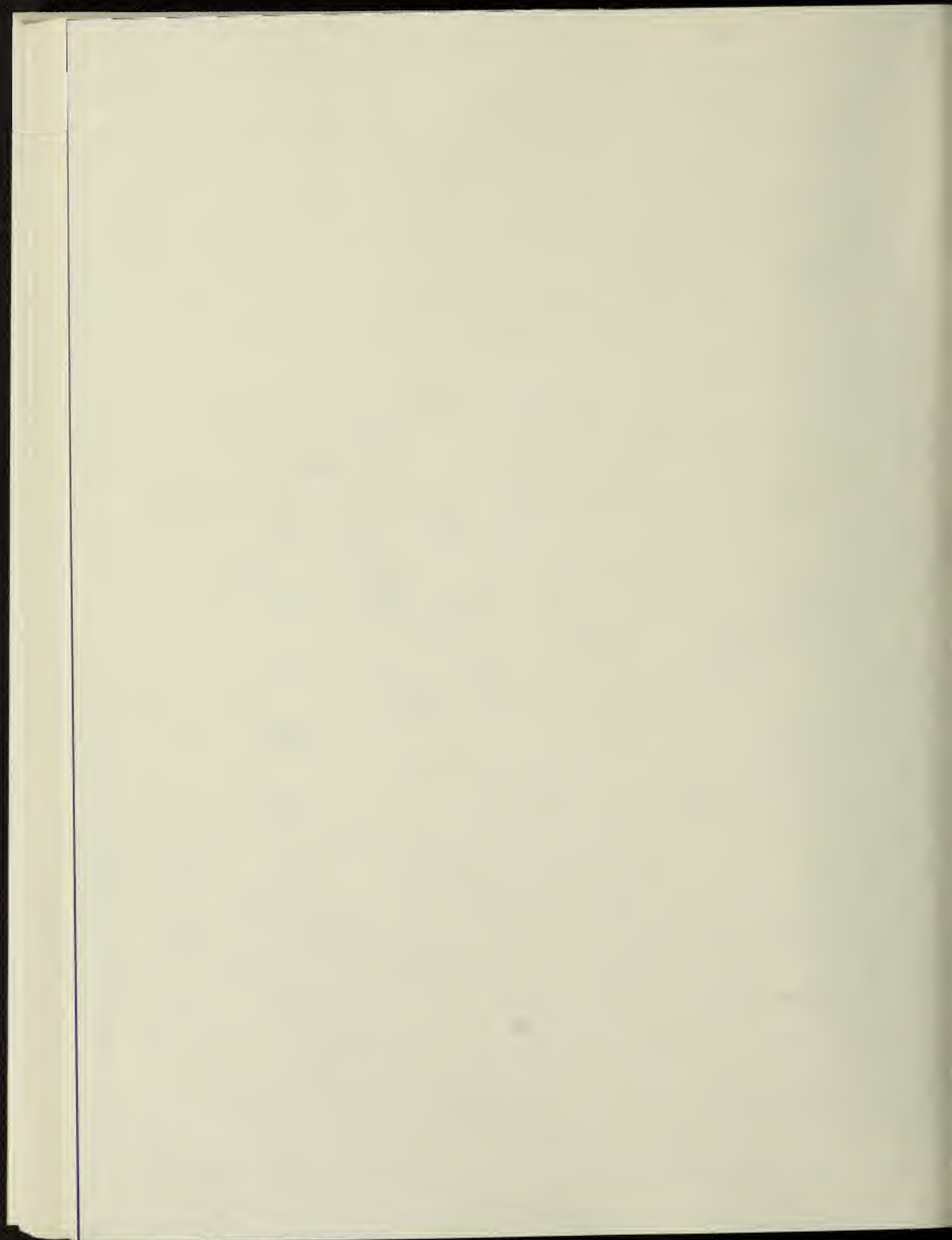
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CARCINOGENESIS ABSTRACTS

VOLUME 17,
ISSUE 2

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CARCINOGENESIS ABSTRACTS

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CARCINOGENESIS ABSTRACTS

VOLUME 17, ISSUE 2

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GENERAL INFORMATION

CARCINOGENESIS ABSTRACTS makes available abstracts, annotations or citations of significant carcinogenesis articles collected from the current major biomedical sources of world literature. This service is provided by the National Cancer Institute through a contract with the Franklin Research Center for preparation of the publication, under Contract No. NOI-CP-75885 with the National Cancer Institute, U.S. Department of Health, Education and Welfare. Published and distributed by the Franklin Institute PressSM.

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ORIGINAL ARTICLES

SYMPTOMS

SYMPTOMS		SYMPTOMS		SYMPTOMS	
1. Headache	2. Dizziness	3. Nausea	4. Vomiting	5. Diarrhea	6. Constipation
7. Stomach pain	8. Abdominal pain	9. Back pain	10. Joint pain	11. Muscle pain	12. Fatigue
13. Weakness	14. Irritability	15. Depression	16. Anxiety	17. Nervousness	18. Sleeplessness
19. Loss of appetite	20. Weight loss	21. Fever	22. Chills	23. Night sweats	24. Pale skin
25. Rapid pulse	26. High blood pressure	27. Low blood pressure	28. Rapid breathing	29. Slow breathing	30. Irregular breathing
31. Increased urination	32. Decreased urination	33. Frequent urination	34. Nocturnal urination	35. Urinary retention	36. Urinary incontinence
37. Urinary pain	38. Urinary odor	39. Urinary color	40. Urinary consistency	41. Urinary volume	42. Urinary pH
43. Urinary specific gravity	44. Urinary sediment	45. Urinary casts	46. Urinary crystals	47. Urinary mucus	48. Urinary blood
49. Urinary pus	50. Urinary leukocytes	51. Urinary erythrocytes	52. Urinary bacteria	53. Urinary fungi	54. Urinary parasites
55. Urinary viruses	56. Urinary toxins	57. Urinary enzymes	58. Urinary hormones	59. Urinary antibodies	60. Urinary antigens

These symptoms are common to many diseases and should be considered in the differential diagnosis of each case. The physician should take a careful history and perform a thorough physical examination to determine the cause of these symptoms. Laboratory tests, such as blood and urine analysis, may be helpful in identifying the underlying condition. Treatment should be directed at the cause of the symptoms rather than the symptoms themselves.

GENERAL INFORMATION

CARCINOGENESIS ABSTRACTS makes available abstracts, annotations, or citations of significant cancer articles collected from the current major biomedical sources of the world literature. This service is provided by the National Cancer Institute through a contract with Franklin Research Center for preparation of the publication.

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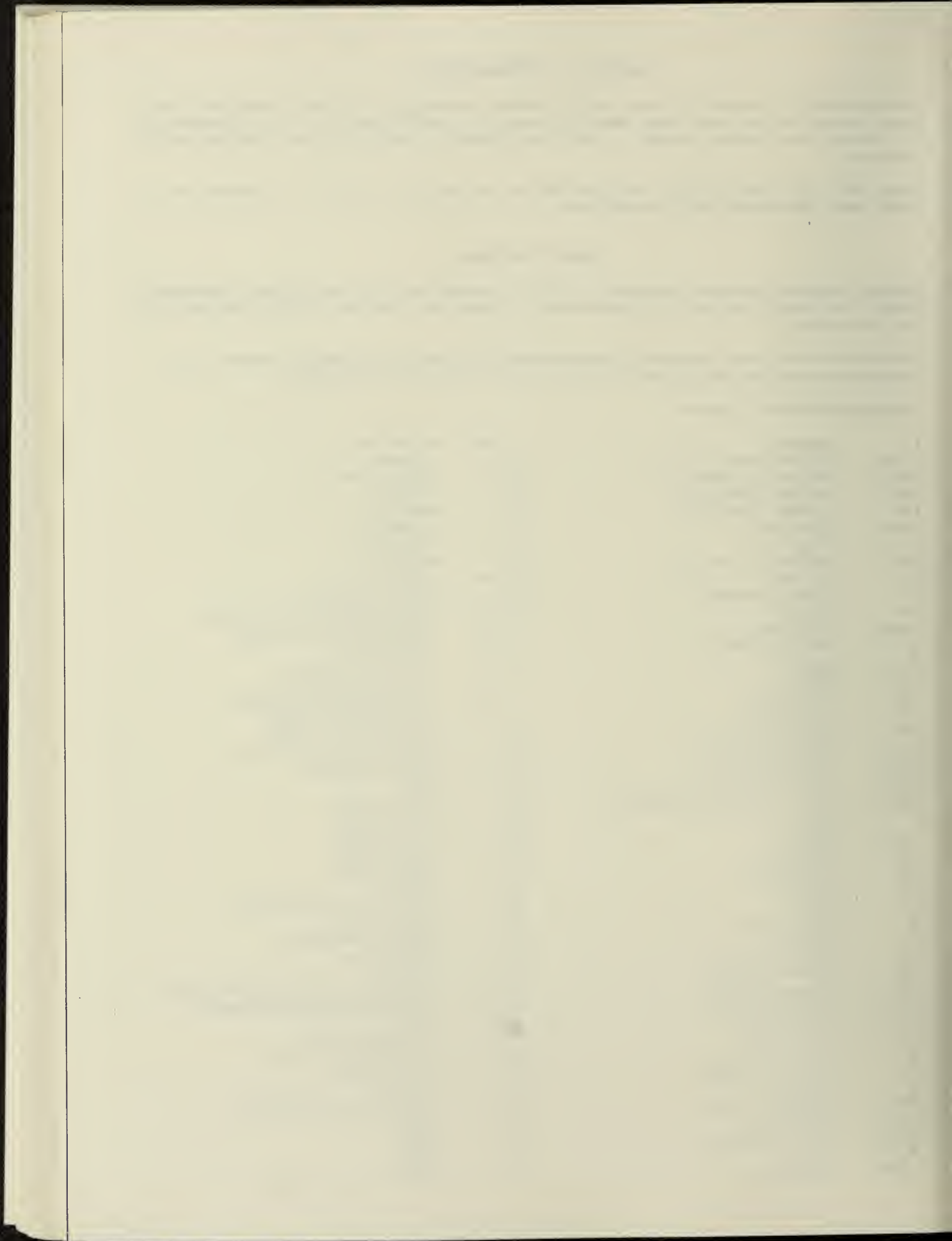
ABBREVIATIONS

JOURNAL names are abbreviated according to the *List of Journals Indexed in Index Medicus, Abbreviation Listing*. If the journal is not listed in this, abbreviations are derived from the *International List of Periodical Title Word Abbreviations*.

LANGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

ABBREVIATIONS used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μl	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μCi	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED ₅₀	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO ₂	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μg	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intradermal	SGOT	serum glutamic-oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT	serum glutamic-pyruvic transaminase
IgB	Immunoglobulin B	soln	solution
IgG	Immunoglobulin G	TCD	tissue culture dose
IgM	Immunoglobulin M	TCD ₅₀	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intraperitoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
Km	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD ₅₀	median lethal dose		
M	molar		
μM	micromolar		



REVIEW

79-0601 Genetic and Related Effects of *Vinca rosea* Alkaloids. (Eng) Degraeve, N. (Laboratoire de Genetique, Universite de Liege, Rue Forgeur 15, B-4000 Liege, Belgium). *Mutat Res* 55(1): 31-42; 1978.

The antitumor properties, stathmokinetic effect, mutagenicity, and teratogenicity of the *Vinca rosea* alkaloids vinblastine (VLB) and vincristine (VCR), together with their effects on DNA and RNA synthesis, chromosomes, and gametogenesis, are reviewed. These compounds appear to be indoleindole dimers in which the indole is linked by a C-C bond to the aromatic ring of the dihydroindole. VLB is used to treat some lymphosarcomas, choriocarcinomas, monocytic leukemias, and Hodgkin's disease, VCR to treat lymphosarcomas, Hodgkin's disease, and acute lymphoblastic leukemias in children. At the cellular level, VLB and VCR produce effects similar to those of colchicine: accumulation of mitotic figures, arrested metaphases with highly coiled chromosomes, multipolar anaphases with lagging chromosomes in the interpolar region, tendency to polyploidy by doubling of the chromosomes but failure of chromatid separation, and, at high concentrations, pyknosis. The alkaloids can bind with nucleic acids, but the bonds disappear at high ionic strength, indicating that they are weakly electrostatic. In cell cultures, both alkaloids inhibit RNA synthesis. VLB interferes with some metabolic reactions related to DNA synthesis. The alkaloids cause chromosome damage in root tips, hamster cell lines, and human lymphocytes. After treatment of mice *in vivo*, VLB and VCR gave a positive response in the micronucleus test. Under specific conditions, it seems that *Vinca* alkaloids can interfere with spermatogenesis. All experiments attempting to demonstrate a mutagenic activity of the two alkaloids yielded negative results. In the hamster, VLB and VCR had a dose-dependent embryocidal effect when injected *iv* on the eighth day of gestation. At doses similar to those used in therapy, there was evidence of gross malformations (microphthalmia, anophthalmia, exencephaly, spina bifida). (81 refs)

79-0602 Describing the Validity of Carcinogen Screening Tests. (Eng) Cooper, J. A. (Div. Cancer Cause and Prevention, NCI, Bethesda, MD, 20014); Saracci, R.; Cole, P. *Br J Cancer* 39(1): 87-89; 1979.

Concepts related to the development and validation of carcinogen screening tests are reviewed. The validity of a screening test is described by its sensitivity (the proportion of carcinogens that give a positive result) and specificity (the proportion of non-carcinogens that give a negative result). The predictive value (PV) of a test (the proportion of carcinogens among the substances that test positive) reflects the sensitivity and specificity of the test and the prevalence (propor-

tion) of carcinogens among the tested substances. As the prevalence changes so does the PV of a program; and the dependence of PV on the specificity becomes stronger as the prevalence declines. Two additional items of information are necessary for the meaningful interpretation of the sensitivity and specificity of a test: the identity of the substances used to evaluate the test and the criterion of a positive test outcome. (8 refs)

79-0603 Butorphanol: A Review of Its Pharmacological Properties and Therapeutic Efficacy. (Eng) Heel, R. C. (Australasian Drug Information Services, P.O. Box 34-030, Auckland 10, New Zealand); Brogden, R. N.; Speight, T.M.; Avery, G. S. *Drugs* 16(6): 473-505; 1978.

The pharmacological properties and therapeutic efficacy of butorphanol (BTP), a synthetic analgesic that is a narcotic agonist and antagonist, are reviewed. In rats given 1 or 2 mg/kg/day BTP *po* for 78 wk, no neoplasms occurred that were not observed with a similar frequency in controls. (67 refs)

79-0604 Genetic Activities of Hycanthone and Some Other Antischistosomal Drugs. (Eng) Ong, T. M. (Natl. Inst. Occupational Safety and Health, ALOSH, Morgantown, WV, 26505). *Mutat Res* 55(1): 43-70; 1978.

The genetic activities of some antischistosomal drugs, particularly hycanthone, are reviewed. Recent studies have shown that hycanthone is a potent mutagen in *Salmonella* and mammalian cells in culture, and that it is mutagenic in several mammalian and submammalian test systems. However, it failed to induce mutations in the mouse specific locus test system. Hycanthone is teratogenic in mice and rabbits. It induces transformation in Rauscher murine leukemia virus-infected mammalian cells and increases the incidence of tumors in schistosome-infected mice and hamsters. The mechanism of mutagenesis and other biological activities probably involves covalent binding of this compound to DNA as well as intercalation between DNA bases. Studies of structure-activity relationships have shown that the mutagenicity of antischistosomal agents can be disassociated from their antischistosomal activity. Lucanthone, niridazole, furapromidium, metrifonate, and oxamniquine have also been shown to be mutagenic in *Salmonella* and/or other test systems. However, data on the mutagenicity and other genetically related activities of these compounds are limited. With the available data for hycanthone, it is difficult to extrapolate its potential mutagenic, teratogenic, and carcinogenic hazard to humans. (138 refs)

- 79-0605 Rotenone: A Possible Environmental Carcinogen (Letter to Editor)?** (Eng) Gosalvez, M. (Bioquímica Experimental, Clínica Puerta Hierro, Universidad Autónoma, Madrid, Spain); Diaz-Gil, J. J. *Eur J Cancer* 14(12): 1403-1404; 1978.

Rotenone, a compound that induces mammary fibroadenomas in albino rats at very low po doses, is widely used in the US and several other countries as an insecticide, pesticide, and piscicide. Ingestion of rotenone by humans through food and drinking water contaminated with this compound may be substantial. Therefore, rotenone should be considered an environmental carcinogen. (9 refs)

- 79-0606 Cytotoxic Effects of Maleic Hydrazide.** (Eng) Swietlinska, Z. (Inst. Biochemistry and Biophysics, Polish Acad. Sciences, 02-532 Warsaw, Rakowiecka 36, Poland); Zuk, J. *Mutat Res* 55(1): 15-30; 1978.

The cytotoxicity of maleic hydrazide (MH), a herbicide and suppressor of plant growth, is reviewed. MH inhibits the synthesis of nucleic acids and proteins in plants and in animal tumor cells. Mutagenicity studies in various systems yielded contradictory results. MH has potent chromosome-breaking activity in plant cells but weak activity in animal cells. MH was carcinogenic to mice and rats in two studies. Plants can break down MH into several products, one of which, hydrazine, is a well-known mutagen and carcinogen. (120 refs)

- 79-0607 Mutagenicity, Carcinogenicity and Teratogenicity of Procarbazine.** (Eng) Lee, I. P. (Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709); Dixon, R. L. *Mutat Res* 55(1): 1-14; 1978.

The mutagenic, carcinogenic, and teratogenic effects of procarbazine (N-isopropyl- α -(methylhydrazino)-p-toluamide: MIH) are reviewed. Experimental and clinical studies strongly suggest that MIH can induce point-mutation chromosomal damage, mutagenicity, antifertility effects, carcinogenicity, and teratogenicity. The molecular mechanism by which it may produce these effects has not been completely elucidated. However, DNA and RNA have been shown to be alkylated at various positions of the nucleotides following exposure to MIH and/or its metabolites. This process has been hypothesized to be a mechanism of mutagenic, carcinogenic, and teratogenic action. Genetic counseling is necessary in any patient exposed to chemotherapeutic agents with mutagenic potential. The antifertility effects of MIH may be reversible or irreversible, depending upon both the dose and duration of chemotherapy, especially in treating Hodgkin's disease. Risks from teratogenic effects of MIH in humans are very small and can easily be circumvented. MIH has been shown to be carcinogenic in experimental animals, but whether this is the case in humans is uncertain. However, reports of secondary

tumors arising in cancer patients during or after chemotherapy are becoming available. Cancer patients receiving combination chemotherapy that includes MIH should be informed of the possible genetic and carcinogenic risks. (99 refs)

- 79-0608 Genetic Material and Cancer: Chemical Carcinogenesis.** (Fre) Zajdela, F. (No affiliation given); Sarasin, A.; Tambourin, P. *Lyon Med* 240(16): 273-280; 1978.

Mechanisms of chemical carcinogenesis are reviewed and related to physical, genetic, and viral carcinogenesis. Theories of DNA repair are explained with the use of illustrative diagrams. (no refs)

- 79-0609 Tumor Promoters: Effects on Proliferation and Differentiation of Cells in Culture.** (Eng) Diamond, L. (Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104); O'Brien, T. G.; Rovera, G. *Life Sci* 23(20): 1979-1988; 1978.

The effects of phorbol diester tumor promoters on the proliferation and differentiation of cells in culture are reviewed, and the relation of these effects to the mechanism of tumor promotion is discussed. Exposures of cells to a phorbol tumor promoter may produce some or all of the following effects: increased prostaglandin, polyamine, RNA, and late DNA synthesis; increased phospholipid metabolism; increased plasminogen activator production; decreased early DNA synthesis; decreased thymidine uptake; decreased expression of large-external-transformation-sensitive (LETS) protein; and altered membrane glycoproteins. Tumor promoters inhibit terminal differentiation of cells in culture, which agrees with in vivo observation that tumor promoters alter normal cell differentiation. Tumor promoters may act by stimulating cell cycling and preventing withdrawal from the cycle into a differentiating pathway. A transient block in differentiation that favors proliferation of the stem cell population could lead to proliferation and amplification of a cell population in which the potential for malignancy had been initiated by a carcinogen but not yet expressed. It is also possible that inhibition of differentiation may be only a secondary result of a more basic effect of tumor promoters on cells that is directly related to their promoting activity. (78 refs)

- 79-0610 The Interaction of Nitrites with Food, Drugs, and Contaminants.** (Eng) Greenland, S. (Div. Epidemiology, Sch. Public Health, Univ. California, Los Angeles, CA, 90024). *J Environ Health* 41(3): 141-143; 1978.

Several thousand compounds occurring in water, food, and medications are capable of reacting with nitrites to produce N-nitroso compounds, a high percentage of which have been

found to be potent carcinogens. Proper controls on food and water levels of nitrites and on the additives and contaminants that react with nitrites must be developed. (34 refs)

79-0611 Carcinogenicity of Benzo(a)pyrene Derivatives: The Bay Region Theory. (Eng) Jerina, D. M. (Natl. Inst. Arthritis, Metabolism and Digestive Diseases, NIH, Bethesda, MD, 20014); Thakker, D. R.; Yagi, H.; Levin, W.; Wood, A. W.; Conney, A. H. *Pure Appl Chem* 50(9/10): 1033-1044; 1978.

Carcinogenicity data for benzo(a)pyrene (BP), benz(a)anthracene (BA), and numerous known and potential metabolites of these polycyclic hydrocarbons (HC's) are reviewed in light of the bay region theory of HC-induced carcinogenicity. The foundation of this theory rests on initial observations of remarkably high chemical reactivity for the epoxide ring in BP diol epoxides. According to the theory, diol epoxides on angular benzo rings of polycyclic HC's, in which the epoxide ring forms part of a "bay region" of the HC, are prime candidates for ultimate carcinogens. The tumor data firmly establish that the 7,8-dihydrodiol of BP and the 3,4-dihydrodiol of BA are proximate carcinogens and that the 7,8-diol 9,10-epoxides and the 3,4-diol 1,2-epoxides are ultimate carcinogens derived metabolically from the respective HC's, and they support the bay region theory. Perturbational molecular orbital calculations indicate that the electronic properties of the π -electron system are responsible for the unusually high chemical reactivity of the diol epoxides. (52 refs)

79-0612 Trends and Reliability of Data on Environmental Cancer. (Eng) Albrecht, R. M. (Bureau Radiological Health, Food and Drug Admin., Rockville, MD, 20857). *J Air Pollut Control Assoc* 29(1): 54-56; 1979.

The reliability of data concerning environmental cancer is considered in relation to presumably authoritative statements regarding environmental causes of cancer. Statistics on cancer incidence may have great deficiencies, especially when comparing (1) developed with underdeveloped countries and (2) incidence and mortality data in developed countries 15-20 yr ago with current data. When two or more agents interact, it is difficult to ascertain and quantify the effect of each; it may not be realistic to attribute a certain cancer to only one agent. There is no realistic common definition of environmental agents, making it difficult to have a common understanding of the quantitative relationship between environmental agents and specific cancers. The estimate that 80%-90% of cancers are environmental and can be prevented is not reliable. It has also been claimed that exogenous and environmental stimuli cause 30%-40% of human cancers. These stimuli include smoking, alcohol, and sunbathing, which should be considered personal habits rather than environmental agents. Several investigators have argued that the lowest reported cancer rates represent baseline or natural rates and that any

surplus is due to environmental agents. The argument would be more persuasive if hard data only were being dealt with. (11 refs)

79-0613 Harmful Effects of Cadmium. (Swe) Elinder, C. G. (Omgivningshygieniska avdelningen, Statens naturvårdsverk, Stockholm, Sweden); Friberg, L.; Piscator, M. *Lakartidningen* 75(47): 4365-4368; 1978.

The environmental and toxicological aspects of cadmium are reviewed. Recent studies show an increased risk of prostate cancer and, possibly, of lung cancer among workers exposed occupationally to certain forms of cadmium. Local sarcomas were found in animals following repeated sc or intratesticular injections of cadmium. (31 refs)

79-0614 Symposium: Awkward Medicolegal Problems in Asbestos-induced Disease. Risk Factors in Asbestosis Exposure. (Eng) Elmes, P. C. (MRC Pneumoconiosis Unit, Llandough Hosp., Penarth, Glamorgan CF6 1XW, Wales). *J R Soc Med* 71(12): 914-916; 1978.

The medicolegal aspects of disease entities resulting from asbestos exposure are discussed from the standpoint of level of exposure. Asbestosis as a cause of serious disabling disease and premature death following high exposure is uncommon now. However, a worker with partial disablement due to asbestosis who is a heavy smoker is at very high (70%-100%) risk of developing lung cancer. A moderate level of asbestos exposure (2-15 fibers/cm³) over a 50-yr working life results in some radiologically identifiable airway changes in most individuals, but the patient's age and smoking habits make the amount of airway disability due to asbestosis debatable. In this individual, the real danger again is from cancer of the lung. The risk of lung cancer in nonsmokers with this occupational history is increased approx fourfold. A heavy smoker has increased his lung cancer risk 10-20 times. Mesothelioma is not of medicolegal importance at moderate exposure levels, as when there is a history of occupational exposure, all cases are 100% attributable. At low continuous or occasional high exposures, lung cancer is probably not a significant risk. Mesothelioma presents the primary medicolegal problem, because it may arise with no accompanying asbestosis or pleural plaques, and occupational exposure may be long since forgotten. (4 refs)

79-0615 Exposure to Asbestos and Its Harmful Effects. A Brief Review. (Nor) Melbostad, E. (Lungeavdelingen, Rikshospitalet, Stockholm, Norway). *Tidsskr Nor Laegeforen* 98(31): 1563-1564; 1978.

Studies on asbestos exposure and the effects of inhaled asbestos are reviewed. Workers handling and processing asbestos

are the most exposed, people living in the vicinity of asbestos mines and of factories where asbestos is used are also exposed. The harmful effects of exposure depend on its intensity and duration and on the type of the fibers; short fibers, such as those of amphibole, are the most hazardous. In terms of harmful effects, short-term intense exposure is equivalent to long-term low-level exposure. Asbestos causes pleural plaques, diffuse interstitial lung fibrosis, lung cancer, and pleural and peritoneal mesotheliomas. The latent period is 3-30 yr, and usually 20-40 yr for mesothelioma. The incidence of lung cancer among workers with asbestosis was 15% in 1947 and rose to over 50% in 1963. Asbestos exposure alone increases the lung cancer risk about fourfold, but exposure with smoking increases the risk by a factor of 92. Although 80%-90% of all mesothelioma patients have been exposed to asbestos, only about 5% of all asbestos-exposed workers develop mesothelioma. The mesothelioma incidence appears to be highest after exposure to crocidolite. There is no relationship between asbestos-induced mesothelioma and smoking. (no refs)

- 79-0616** **Implanted Polymers.** (Eng) Bagnall, R. (ICI Pharmaceuticals Div., Hurdsfield Industrial Estate, Macclesfield, Cheshire SK10 2NA, England). *Chem Br* 14(12): 598-602; 1978.

Physical properties appear to play a major role in determining the biocompatibility of implanted polymers. Implant shape (sharp corners or edges), rigidity, and surface roughness can all induce excess collagen synthesis, and small particles caused by wear may produce a reaction similar to the fibrogenic response to inorganic dusts. Large, nonporous implants have induced tumors in rodents at the implant site after 6 mo, an effect called solid state or foreign body carcinogenesis. These tumors have not been reported in humans, in spite of the use of large implants such as mammary prostheses. (17 refs)

- 79-0617** **Skin Cancer.** (Spa) Galvan Aguilera, A. S. (Fundacion para el Diagnostico Temprano del Cancer, A. C. Av. Oaxaca 96-202, Mexico 7, D.F., Mexico). *Patol Quir Citol Esfoliativa* 4(4): 145-153; 1978.

The epidemiological, clinical, histopathological, prophylactic, and therapeutic aspects of skin cancer are reviewed. Skin cancer affects slightly more men than women, mainly at advanced age. It is more frequent in white than in dark-skinned or black races; the incidence is highest among whites living in tropical areas, such as Australia and New Zealand. The mortality per 100,000 was 7.1 in Australia, 6.7 in New Zealand, 4.6 in Switzerland, 4.5 in Denmark, 4.0 in Czechoslovakia and the USA, 3.4 in France, 1.5 in Mexico, 1.3 in Japan, 0.6 in El Salvador, 0.5 in Panama, 0.3 in Honduras, and 0.1 in Thailand in 1972-1973. The most common types of skin cancer are basal-cell carcinoma, epidermoid car-

cinoma and malignant melanoma. The epidemiological data show a clear correlation between skin-cancer mortality and intense exposure to UV radiation. (11 refs)

- 79-0618** **Photoreactivation in Mammalian Cells.** (Eng) Sutherland, B. M. (Biology Dept., Brookhaven Natl. Lab., Upton, NY, 11973). *Int Rev Cytol Suppl* 8: 301-334; 1978.

Cellular photoreactivation (PR) phenomena and the properties and function of photoreactivating enzymes (PRE's) are reviewed, along with the role of PR in the repair of UV damage in humans. PRE deficiencies (0%-50% of normal level) have been found in xeroderma pigmentosum (XP) cells, and true defects in PRE's are reflected by a lower rate of PR in XP cells with similar backgrounds of other repair processes. Investigations revealed that some XP patients were normal in excision repair but had defects in other repair processes. Others seemed to be deficient in excision and postreplication repair, PR, and in an enzyme nicking the phosphodiester backbone at depurination sites. In PR and in excision, defects can be detected in individuals normal with respect to sun sensitivity or solar carcinogenesis (CG). A simplified scheme for explaining these apparent contradictions is a proposal for summing the cell's total repair capacity. In this scheme, excision and postreplication repair and PR are weighted equally. In spite of several drawbacks, the scheme has two appealing features: all repair parameters are measurable and can be compared to clinical manifestations of solar CG, a good correlation between repair defects and CG is apparently provided. Concerning the origin of repair defects, there does not seem to be a general defect in messenger RNA or protein synthesis leading to abnormalities of many proteins. The possibility of coordinate control of repair processes is attractive and may explain the existence of multiple repair defects. Several lines of evidence indicate that repair enzyme levels are regulated in cells. There does not seem to be a correlation in the number of repair defects in cells with multiple repair defects. (84 refs)

- 79-0619** **Symposium on Photochemotherapy (PUVA). Possible Long-Term Hazards of Photochemotherapy with Psoralens and Near Ultraviolet Light.** (Eng) Bridges, B. A. (MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton BN1 9QG, England). *Clin Exp Dermatol* 3(4): 349-353; 1978.

The advisability of using photochemotherapy with psoralens and near UV (A) radiation (PUVA) is weighed against its cytotoxic and genotoxic hazards. According to current criteria, PUVA must be regarded as an established skin carcinogen in mice. In humans, the only published evidence for carcinogenicity comes from experience with four xeroderma pigmentosum patients, who showed an accelerated rate of

appearance of skin tumors within 1 mo of starting treatment with trimethylpsoralen. (21 refs)

- 79-0620 Postirradiation Neoplasia: A Symposium.** (Eng) Scanlon, F. (Dept. Surgery, Evanston Hosp., Evanston, IL); Berk, R. S.; Khandekar, J. D. *In: Curr Probl Cancer* 3(6): 45 pp.; 1978.

The literature concerning radiation carcinogenesis, specifically, the development of thyroid, bone marrow, skin, parathyroid gland, salivary gland, breast, lung, head and neck, pelvic, and pediatric tumors plus Hodgkin's disease and sarcomas, is reviewed. A large amount of evidence suggests that radiation given in infancy and childhood is etiologically related to subsequent development of carcinoma in the head and neck. Apparently, very high doses of radiation are less likely to be carcinogenic than lesser amounts. Very small doses are probably not carcinogenic either. In general, the younger the patient at the time of irradiation, the greater the risk of subsequent development of carcinoma. However, the breast seems to be an exception, as it is more sensitive to radiation-induced carcinogenesis between the ages of 10 and 35. Chronic low doses of radiation seem to be particularly carcinogenic in humans. The latent interval between irradiation and the appearance of carcinoma in most sites averages about 30 yr. Leukemia, however, usually appears 5-8 yr after irradiation. Irradiation for malignant tumors in all parts of the body probably predisposes to the later development of irradiation carcinoma in long-term survivors. Radiation-treated patients should be followed carefully for life. (151 refs)

- 79-0621 Non-A and Non-B Viral Hepatitis.** (Ita) Rossolini, A. (Istituto di Clinica delle Malattie Infettive, Università Siena, Siena, Italy); Almi, P.; Cellesi, C.; Figura, N. *Recent Prog Med (Roma)* 64(4): 391-403; 1978.

Studies of hepatitis induced by herpes simplex virus (HSV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) are reviewed. Compared with the incidence of HSV infections, HSV-induced hepatitis is rare, affecting mainly undernourished subjects, patients with severe infectious diseases, and patients with immunodeficiency. The incidence of CMV-induced hepatitis has shown a recent increase due to the widespread use of blood transfusion and immunosuppressive therapy. Infectious mononucleosis associated with EBV-induced hepatitis can be due to oral transmission or, in an increasing number of cases, to blood transfusion. (41 refs)

- 79-0622 Virus and Human Cancers.** (Fre) Van Tieghem, N. (Laboratoire de Microbiologie et d'Immunologie, Faculté de Médecine de Bruxelles, Brussels, Belgium). *Brux Med* 58(10): 551-561; 1978.

Experimental and theoretical evidence for the relationship of viruses to human cancer is reviewed. Criteria for oncogenicity, and the biological, biochemical, morphological, and immunological properties of DNA and RNA viruses responsible for animal and human tumors are outlined. (no refs)

- 79-0623 Leukemia and Lymphoma: Infrequent Manifestations of Common Viral Infections? A Review.**

(Eng) Francis, D. P. (Hepatitis Lab. Div., Center Disease Control, 4402 N. 7th St., Phoenix, AR, 85014); Essex, M. *J Infect Dis* 138(6): 916-923; 1978.

The clinical, virologic, and epidemiologic aspects of feline leukemia virus (FeLV) are reviewed with emphasis on factors that are most applicable to the search for cancer-causing viruses in humans. After an incubation period of 2-4 wk, FeLV causes a relatively mild infection; a small number of infected cats (44/100,000) develop leukemia or lymphoma months or years after the initial infection. Most cats exposed to FeLV produce both neutralizing antibodies and feline oncornavirus membrane-associated antigen (FOCMA) antibodies and suffer no complications. Animals that do not produce antibodies develop a persistent viremia and often tumors. Thus, failure to detect antibodies to suspected virus-induced antigens in humans with cancer is not surprising. Neither is the failure to detect virus, viral particles, viral structural antigens, or viral genetic sequences, since oncogenic viruses can infect a host and induce a malignancy without producing infectious virus. The identification of cancer-causing viruses is also complicated by the requirement for other factors in addition to the etiologic agent for tumor induction, eg, immunosuppression, age at infection, and genetic background. Emphasis should be placed on establishing a link between human lymphoreticular cancer and retroviruses and/or DNA viruses. (32 refs)

- 79-0624 From Experimental Animal Models to Human Lymphoid Tissue Neoplasia: Search for a Viral Etiology.** (Eng) Kaplan, H. S. (Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305). *In: Recent Results Cancer Res* 64: 325-336; 1978.

Experimental studies of laboratory mammals have offered many clues to the etiology and pathogenesis of human lymphomas and leukemias, including the observation that viruses are the universal etiologic agents of these neoplasms in all mammalian species studied to date, with ionizing radiation and chemical leukemogens serving to activate latent leukemogenic viruses rather than cause somatic mutation. The possibility of the existence of human leukemia-lymphoma viruses is very real, but in order to be conclusively proven as such, any suspect virus must successfully meet a stepwise series of criteria. Some of these steps are demonstrated by a C-type RNA virus isolated from a cell line (SU-DHL-1) established by culturing tumor cells from dif-

fuse histiocytic lymphoma patients. The virus contains 70S RNA, reverse transcriptase (RT) activity, and has an equilibrium density of approx 1.15 g/ml in sucrose gradients. It has the capacity to induce syncytia in rat XC cells and, electron microscopically, it resembles other mammalian C-type RNA viruses in size and morphology. Studies of the inhibition of its RT activity by antibodies to the RT's of other C-type RNA viruses suggest some degree of relatedness to subhuman primate viruses. The virus failed to propagate on various fibroblastic and other nonlymphoid indicator cell lines. However, the addition of filtered virus preparations to fresh human buffy coat mononuclear (or normal human spleen) cell cultures or to the adherent cells from these cultures (initially composed almost entirely of monocytes and later of macrophages) caused reproducible changes in the growth behavior and culture morphology of the infected normal human cells. Cells bearing aneuploid chromosome complements were observed in some of these cultures after 1-4 wk, similar to cultures of rhesus monkey buffy coat cells. Additional in vitro studies in progress should determine whether the virus has lymphoma-inducing potential for normal human cells of the corresponding cell type. Demonstration that the virus is human will require careful biochemical and seroepidemiologic studies. (58 refs)

79-0625 Recent Data on the Pathogenic Role of Epstein-Barr Virus (EBV). (Fre) Seigneurin, J. M. (Laboratoire de Virologie, C.H.U. de Grenoble, BP 217 X, F 38043 Grenoble Cedex, France); Lenoir, G. *Nouv Presse Med* 7(44): 4003-4004, 1978.

EBV has been demonstrated to be the cause of infectious mononucleosis, but its role in Burkitt's lymphoma and nasopharyngeal carcinoma has not yet been fully proved. There is an evident genetic predisposition toward nasopharyngeal carcinoma. (7 refs)

79-0626 Mechanisms and Abnormalities of Immune Regulation. (Eng) Russell, I. J. (Dept. Immunology, Mayo Medical Sch., Rochester, MN, 55901); Tomasi, T. B. *Pathobiol Annu* 8: 1-33; 1978.

Current concepts regarding the mechanisms that regulate antibody production are reviewed, and some exemplary diseases in which regulation may be abnormal are identified. Specific topics include (1) the interactions of macrophages and lymphocytes, cells involved in the humoral immune response; (2) soluble factors that modify immunoglobulin (Ig) synthesis or replace certain necessary cell-mediated functions; and (3) the relevance of the abnormality of these mechanisms to selected immune diseases. Until recently, most defects in immune-deficiency syndromes were explained on the basis of developmental defects in the B cells. However, certain immune disorders may be based on imbalances between regulatory cells; ie, helper, suppressor, and amplifier T cells, as well

as macrophages. It is the net or algebraic sum of the various regulatory positive and negative influences that determines the magnitude of the resulting immune response. In some diseases, however, the initiating event may secondarily lead to a regulator abnormality that subsequently perpetuates the disease. The characteristics of X-linked hypogammaglobulinemia, common variable immunodeficiency, the secondary hypogammaglobulinemia seen in multiple myeloma, rheumatoid arthritis, sarcoidosis, chronic active hepatitis, and systemic lupus erythematosus are described. Elaboration of soluble amplifiers and suppressors of Ig synthesis by normal mammalian cells requires exogenous stimulation by mitogens and certain antigens. In contrast, amplifier materials are produced spontaneously by cells from certain patients with certain autoimmune diseases. It may be that they are activated by an as yet unknown antigenic challenge, such as self-antigens modified by an extrinsic agent such as a virus. The molecular size and properties of soluble factors are outlined to stress both the similarities and heterogeneity of the products obtained from different systems. Factors found in disease states may represent normal mechanisms operating in an abnormal or uncontrolled manner. (122 refs)

79-0627 Problems in Defining the Nude Mouse. (Eng) Rygaard, J. (Pathological-anatomical Inst., Municipal Hosp., Copenhagen K, Denmark). *Folia Biol (Praha)* 24(5): 289-299; 1978.

Several discrepancies among nude mice are reviewed with respect to their influence on studies using these animals. For example, the amount of genetic material showing accordance between the background strain, heterozygous $nu/+$ or homozygous nu/nu , is not known; this is particularly important in reconstitution experiments or in mixed lymphocyte culture tests. Immunoglobulin (Ig) levels in nude mice, particularly IgG and IgA levels, are different in various laboratories due to the genetic background of the mice used and the milieu in which they live. Nude mice have been used for the heterotransplantation of a large number of human tumors, and the take rate is approx 35%. Although the successful transplants have garnered the most attention, the unsuccessful transplants raise several interesting questions concerning whether the tumors are thymus-dependent or -independent; the role of macrophages, natural killer cells; and specific antibodies; and the effect of cytostatic drugs or x-irradiation. Following transplantation into nude mice, tumors that metastasize and kill their human host usually adopt a benign behavior. A few transplanted human tumors will metastasize in nude mice; most will not. In spite of these and other discrepancies and unanswered questions, many questions have also been resolved with the use of the nude mouse, such as the diversity of B cells, the nature of B-cell mitogens, and the specificity and role of T cells in immunology. (43 refs)

79-0628 Lymphomagenesis and Autoimmunization Caused by Reactions of T-Lymphocytes to Incompatible Structures of the Major Histocompatibility Com-

plex: A Concept of Pathogenesis. (Eng) Gleichmann, E. (Dept. Immunohistopathology, Central Lab. Netherlands Red Cross Blood Transfusion Service, Univ. Amsterdam, P.O. Box 9190, Amsterdam, Netherlands); Melief, C. J.; Gleichmann, H. *In: Recent Results Cancer Res* 64: 292-315; 1978.

Since T-cell anti-major histocompatibility complex (MHC) reactions comparable to those seen during the graft-vs-host reaction (GVHR) may also occur in an autologous system, it has been postulated that they may lead to the same diseases as in the semiallogeneic parent- F_1 hybrid system. This hypothesis is reexamined in light of recent findings. In F_1 hybrids undergoing chronic GVHR, autoantibody formation is triggered by the abnormal assistance provided to normally present but inactive autoreactive B cells of the F_1 recipient by donor T cells reacting to their incompatible H-2 structures (allogeneic effect). A related immunologic mechanism (back-stimulation) may be responsible for the proliferation of H-2-incompatible F_1 B cells in the presence of donor T cells. Persistent proliferation, mainly of F_1 B cells, leads to immunoblastic sarcomas in GVH F_1 mice. It is not known whether GVH-induced lymphomas develop independently of C-type RNA viruses or whether lymphoid tissues stimulated by chronic GVHR provide a favored microenvironment for viruses of otherwise low oncogenicity. GVH lymphomagenesis may also be caused by C-type RNA viruses for which an assay has not been developed. However, two lines of evidence support the above hypothesis: (1) results obtained with animal GVH models, in which immunoblastic sarcoma, angiogenesis, and autoantibody formation were induced by reactions of parental T lymphocytes toward genetically incompatible MHC structures; (2) recent discoveries pointing to similarity in T-cell reactions toward genetically foreign MHC structures on the one hand and self-MHC structures on cells rendered foreign by chemicals or infectious agents on the other. This concept implies that small numbers of T lymphocytes are crucial for the pathogenesis of certain lymphomas that, according to current nomenclature and thinking, are thought to be exclusively disorders of B lymphocytes. (168 refs)

79-0629 The Contribution of Electron Microscopy to the Diagnosis of Tumors. (Eng) Mackay, B. (Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Osborne, B. M. *Pathobiol Annu* 8: 359-405; 1978.

The value of electron microscopy (EM) in tumor diagnosis is demonstrated by a review of cases studied at the M. D. Anderson Hospital in Houston, Texas. The cases discussed are grouped under three broad headings, carcinomas, small round cell tumors, and sarcomas. Carcinomas illustrate both the practical value of EM in solving diagnostic problems and its limitations. EM can lead to a specific diagnosis or it may offer no information that cannot be obtained from light microscopy (LM). However, most cases fall somewhere in between, and EM studies may narrow a differential diagnosis

or provide reassurance by confirming a LM impression. Small round cell tumors are often difficult to identify by LM because of their morphologic similarity. This is an area in which EM can offer a significant contribution in almost every case. Problems in identifying sarcomas are often encountered at the LM level, and EM studies can lead to enhanced precision in diagnosis and subclassification. However, the clinical significance of the contribution may be less than that in the other two groups with regard to prediction of biologic behavior and influence on selection of therapy. Despite its variable contribution, EM can be helpful in most problem cases if good material is available for study and when findings are correlated with the light microscopic histology and the available clinical information. (174 refs)

79-0630 Cell Cycle. General Aspects. (Spa) Galanti, N. (Unidad de Biología Celular, Universidad de Chile, Santiago de Chile, Chile). *Rev Med Chil* 105(12): 927-933; 1977.

Studies on the cell cycle are reviewed with special regard to hyperplasia. The cell cycle is regarded as a biological system in which the control mechanisms that ensure the orderly performance of cell growth, differentiation, and organ maintenance exert their effects. Thus, in the cell cycle the cells may go from one mitosis to the next, or leave the proliferative cycle in G_1 or R_2 , from the resting states (G_0 or R_1), the cells may return to the proliferative cycle, or undergo irreversible differentiation. Considering these possibilities, hyperplasia may be due to 1) a shortening of the proliferative cycle; 2) a shift of cells from the resting state to the cycle; 3) a decrease in cell loss, and/or 4) the influx of cells from populations other than the original. Experiments have shown that the cell cycle time in normal tissues and tumor tissues (Ehrlich ascites tumor; C3H breast tumor; bronchial, gastric, and endometrial carcinoma; acute myelogenous leukemia; HeLa cells and glioma cells) is practically of the same order of magnitude. Thus, hyperplasia results from the recruitment of resting cells and/or from a decrease in the rate of cell loss, rather than from a shortening of the proliferative cycle. In keeping with this finding, recent investigations tend to concentrate on the mechanisms responsible for the G_0 to G_1 transition and on the processes of cell aging and death, rather than on the factors responsible for changing the length of the cell cycle. (34 refs)

79-0631 On the Terms "Reticulosis" and "Reticulum Cell Sarcoma" with Regard to the Modern Concept of the Monocyte Macrophage System. (Eng) Leder, L. D. (Institutes für Pathologie, Westdeutsches Tumorzentrum, Universität Essen, Hufelandstrasse 55, D-4300 Essen 1, W. Germany). *Klin Wochenschr* 56(22): 1091-1096; 1978.

The monocyte macrophage system has replaced the concept of the reticuloendothelial system, and it is not independent

of but is closely related to the myeloid system. All reticulososes have been found to belong to the myeloid or lymphatic system, and most reticulum cell sarcomas or malignant histiocytic lymphomas seem to be of lymphatic rather than macrophage origin, representing high-grade malignant lymphomas, possibly immunoblastic sarcomas. Thus, the use of reticulosis and reticulum cell sarcoma is meaningless and confusing, since the concepts upon which these terms are based are no longer tenable. (42 refs)

79-0632 Surface Morphology of Lymphoreticular Cells: Review of Data Obtained from Scanning Electron Microscopy. (Eng) Polliack, A. (Dept. Hematology, Hadassah Univ. Hosp., Hadassah Medical Sch., Jerusalem, Israel). In: *Recent Results Cancer Res* 64: 66-93; 1978.

Scanning electron microscope (SEM) studies of the surface morphology of normal and malignant lymphocytes and other WBC are reviewed. Normal lymphocytes can be distinguished from monocytes and macrophages on the basis of their surface architecture. Lymphocytes have fingerlike microvilli and generally lack ruffles, but monocytes and macrophages lack multiple microvilli and have broad-based ruffles. Although B and T lymphocytes have a different surface morphology, as proved by other modes of microscopy and cryofracture, they should not be distinguished solely on the basis of number of microvilli seen under the SEM. Circulating leukemic lymphocytes and Sezary cells show a spectrum of surface morphology with varying numbers of microvilli. Leukemic lymphoblasts may also occasionally show microvilli, but more frequently they lack them or display only a small number. Ruffles are rarely encountered in all these leukemic cell types. Plasma/myeloma cells have surface blebs and microvilli, but hairy cells are readily distinguished from chronic lymphocytic leukemia cells by the presence of ruffles and clusters of microvilli. In some cases of histiocytic lymphoma, cells have well-developed ruffled membranes resembling those seen on monocytes and monoblasts, but in other cases cells are lymphoid and display multiple microvilli. In most cases, myelo/mono/myelomonocytic cells are readily distinguished from lymphocytic cells on the basis of surface architecture and are characterized by raised ridgelike profiles and/or prominent ruffled membranes. SEM is a useful adjunct to other modes of microscopy, and it may contribute to the diagnosis of lymphoreticular and leukemic disorders. (106 refs)

79-0633 Cell Surface Structures, Differentiation and Malignancy in the Haemopoietic System. (Eng) Greaves, M. (Membrane Immunology Lab., Imperial Cancer Res. Fund, Lincoln's Inn Fields, London, England). In: *Symp Soc Exp Biol* 32: 429-442; 1978.

Studies of the role of cell-surface events in hematopoietic differentiation and maturation using human leukemic cells are

reviewed. Most of the acute nonmyeloid leukemias that appear lymphoid or "undifferentiated" do not appear to express specific gene products of T and B lymphocytes (T-cell antigens and immunoglobulin, respectively) on their surface. Therefore, acute lymphoblastic leukemia (ALL) cells are likely frozen at an earlier pre-T, pre-B stage of development. Studies of chronic myeloid leukemia (CML) have suggested that (1) CML can frequently involve transformation of a pluripotent stem cell; (2) since Philadelphia chromosome (Ph⁺)-positive and Ph⁺-negative leukemias can have similar or identical phenotypes, the phenotype components (eg, membrane antigens) are reflections of normal gene activity; ie, they are precursor or stem cell markers; (3) CML can be used as a monoclonal system to map normal cellular relationships and developmental sequences in hematopoiesis (HP). The ALL and Ia-like antigens are believed to be normal gene products of the target stem cells for acute leukemia transformation, and they may play an important role in early HP. It is hypothesized that malignancy and regeneration involve selective proliferation of stem cells that are more common in fetuses and children than in adults and that the antigenic properties of these cells are effectively normal; ie, ALL and Ia-like antigens are normal stem cell antigens. It is suggested that ALL⁺ cells are not myeloid progenitors and that IA is expressed on at least some stem cells committed to the granulocytic-macrophage pathway. Clinical evidence suggests that T cells can regulate hemopoietic development (of granulocytic and erythroid lineages). Regulatory cell interactions controlled by the major histocompatibility gene locus may have a central significance in HP and may not be restricted to mature immunocompetent cells. (64 refs)

79-0634 A History of the Reed-Sternberg Cell. (Eng) Taylor, C. R. (Section Immunopathology, Los Angeles County/USC Medical Center, 2025 Zonal Ave., Los Angeles, CA, 90033). *Biomedicine* 28(4): 196-203; 1978.

The evidence of a possibly histocytic or lymphocytic origin of the Reed-Sternberg cell is reviewed, along with implications of a lymphocytic origin. The concepts presented indicate that the different histological forms of lymphoma (including Hodgkin's disease) are not indicative of a different cellular origin, but merely reflect (1) the radical morphological and functional changes expressed by a single progenitor cell, the lymphocyte, during its proliferation cycle and (2) the overall kinetics of the neoplastic lymphocyte population. (85 refs)

79-0635 Monitoring Disease in England and Wales: Methods Applicable to Routine Data-Collecting Systems. (Eng) Fraser, P. (London Sch. Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, England); Beral, V.; Chilvers, C. *J Epidemiol Commun Health* 32(4): 294-302; 1978.

Routine data-collecting systems and methods for disease surveillance in England and Wales are reviewed. Population-based correlation studies are being made to try to explain

disease trends by relating routine health statistics to possible causative agents on a secular, geographical, or occupational basis. In addition, information collected by routine general-purpose systems is being linked as a means of identifying and following individuals exposed to potential hazards. (49 refs)

- 79-0636 Cancer of the Colon and Rectum.** (Swe) Holmstrom, B. (Kirurgiska kliniken, Serafimerlasaret, S-112 83 Stockholm, Sweden). *Lakartidningen* 75(46): 4266-4268; 1978.

The etiological, epidemiological, clinical, and therapeutic aspects of cancer of the colon and rectum are described. A high correlation was found between cancer of the colon and rectum and high fecal bile acids and Clostridia content. Cancers of the colon and rectum account for 7.8% and 4.8% of all malignant tumors, respectively, in men, and for 8.3% and 3.6%, respectively, in women. (5 refs)

- 79-0637 Early Diagnosis of Cancer.** (Spa) Schulz Contreras, M. (Patologia de la Facultad de Medicina, U.N.A.M., Mexico); Castillo Nava, J.; Cervantes, L.; Gaitan Galarza, V.; Paredes Aguilera, R.; del Rio Huidobro, J. *Patol Quir Citol Esfoliativa* 4(1): 3-26; 1978.

Studies of carcinogenic agents, cancer epidemiology, and the early diagnosis of cancer are reviewed. The overall cancer mortality appears to be significantly higher in Northern European countries (Scotland, Luxembourg, England, Wales, and Finland) than in tropical countries (294-332/100,000 vs 40-137/100,000). A positive correlation was found between the gastric cancer incidence and the consumption of smoked meat and fish, and a negative correlation was found between the consumption of a diet rich in wheat products and antioxidant-containing preservatives. A positive correlation was found between low-roughage diet and cancer of the colon, because low-roughage food passes through the bowels more slowly than does food rich in fibers so that the intestinal mucosa is exposed to carcinogens for a prolonged period. The low incidence of cancer of the penis in circumcised men and of cervical cancer in their spouses is believed to be linked not only with the absence of the carcinogenic smegma factor but also with higher hygienic standards. (no refs)

- 79-0638 Pineal Gland, F.S.H., and Breast-Cancer Aetiology (Letter to Editor).** (Eng) Adami, H. O. (Dept. Surgery, Univ. Hosp., S-750 14 Uppsala, Sweden); Rimsten, A.; Wide, L. *Lancet* 2(8103): 1312-1313; 1978.

Data contradicting a role for the pineal gland in the etiology of breast cancer are presented. An androgenic rather than an estrogenic predominance was found in one study of postmenopausal (pm) women with breast cancer, and in another, serum follicle-stimulating hormone (FSH) values did not differ in the patient and control groups. In addition, the pm ovary loses its capacity to respond to FSH by estrogen secre-

tion, and pm estrogen production is accounted for almost exclusively by peripheral metabolism of the androgenic precursors, mainly derived from the adrenals. (5 refs)

- 79-0639 Thyroid Disease in Relation to Breast Cancer.** (Eng) Vorherr, H. (Dept. Obstetrics-Gynecology, Univ. New Mexico, Sch. Medicine, 915 Stanford Dr. N. E., Albuquerque, NM, 87131). *Klin Wochenschr* 56(23): 1139-1145; 1978.

The relationship of thyroid disease to human breast cancer is reviewed. There have been suggestions that hypothyroidism may protect women from breast cancer and, conversely, that it may be associated with an increased risk of breast cancer. It has been hypothesized that a deficiency in circulating thyroid hormones hypersensitizes the mammary glandular epithelium toward prolactin and estrogens, thereby aiding in the development of breast neoplasia. Although there is some data indicating that thyroid hormone replacement therapy increases the risk of breast cancer, this has been contested and the American Thyroid Association recommends that hypothyroid patients should take replacement medication if indicated. The metabolic effects of thyroid hormone in hyperthyroid conditions have been described as protecting against breast cancer, but the possibility of a thyroid hormone-induced increase in estrogen activity, with an enhanced risk of breast cancer, also seems to exist. Thus, the role of thyroid hormone in the development and/or growth of breast cancer remains undefined. The controversy can be satisfactorily resolved only by a prospective study, preferably of postmenopausal women, correlating thyroid, pituitary, and adrenocortical function with estrogen status and the results of periodic breast and genital examinations. (67 refs)

- 79-0640 Epidemiology of Breast Cancer.** (Eng) Saracci, R. (Unit Epidemiology and Biostatistics, International Agency Res. Cancer, 150 Cours Albert-Thomas, 69008, Lyon, France); Repetto, F. In: *Semin Oncol* 5(4): 342-350; 1978.

Epidemiological data on breast cancer (BC) are reviewed. After skin cancer, BC is the most frequent cancer in women of Western countries. High rates are found in Northern and Western Europe and North America, low rates in Africa, Latin America, and Asia, and intermediate rates in Eastern and Southern Europe. The age-incidence curve in Western countries shows two peaks, one at approx age 45 and another much later, indicative of both a premenopausal (related to ovarian activity) and a postmenopausal (accounting for approx two-thirds of cases) type of BC. Approx 10%-15% of BC's show familial aggregation, particularly the premenopausal, bilateral type. No firm association has been detected between BC and various genetic markers, but of current interest are markers specifically related to possible steps in the pathogenesis of BC. Theories largely involve the hormone composition of women, and several observations indicate that BC risk is directly related to duration of menstrual life, with its cyclic elevations of hormone (particularly estro-

gens) levels. In this regard, the estriol (E_3) ratio hypothesis appears to explain many well-documented features of BC. However, no pattern of hormone production or hormone milieu has been firmly established in relation to BC risk. Environmental factors, such as ionizing radiation, long-term use of reserpine, intake of high-fat diet, and presence of an apparently B-type RNA virus in human milk, have all been implicated in BC development to varying degrees. In brief, the current emphasis is on multicausality, including genetic, hormonal, nutritional, viral, and other environmental elements, as the key to understanding BC etiology. (19 refs)

- 79-0641** **Circumcision in the Prophylaxis of Cancer of the Penis and Uterine Cervix.** (Por) Tractenberg, M. (No affiliation given); Gindin, L. R. *Psicanalis da Circuncisao* 111-137; 1977.

Literature on the significance of circumcision in the prevention of cancer of the penis and uterine cervix is reviewed. Even though the smegma seems to contain carcinogenic components, the prophylactic value of circumcision does not appear clearly from the literature. Most authors believe that adequate hygiene of the genitals in both sexes is a more effective prophylactic measure than circumcision. Consequently, routine prophylactic circumcision is unjustified and inhumane due to its ineffectiveness and possible intraoperative and postoperative complications. (31 refs)

- 79-0642** **The Management of Tumors of the Upper Cervical Spine.** (Eng) Dunn, E. J. (Fallon Clinic, Inc., 630 Plantation St., Worcester, MA, 01505); Anas, P. P. *Orthop Clin North Am* 9(4): 1065-1080; 1978.

The management of benign and malignant tumors of the atlas and axis is discussed. Of the 28 atlantoaxial tumors reported in the literature, two-thirds were metastatic, the most common primaries being lung, breast, prostate, and thyroid cancers, myeloma and lymphoma. Primary atlantoaxial tumors included chordoma, osteochondroma, giant cell tumors, osteoid osteoma, aneurysmal bone cysts, and osteogenic sarcoma. Vigorous therapeutic measures should be aimed at completely ameliorating pain, reversing neurologic impairment, and attaining cervical stability. The transpharyngeal needle biopsy of Ottolenghi is a safe and dependable method for obtaining tissue for diagnosis from the anterior elements of C1 and C2. Cervical myelography is necessary to distinguish between the two basic mechanisms that are responsible for cord compression. Flexion and extension views, cineradiography, angiography, and tomography may further assist in patient evaluation. Anterior surgery in this region should be reserved for patients with benign tumors or cancer patients with a good prognosis and specific indications. Tracheostomy should be performed to avoid postoperative complications after anterior surgery. Most patients with metastatic disease are not surgical candidates, but many are helped by radiation therapy, chemotherapy, and a soft cervical collar or other

conservative external immobilization devices. Bone grafting should be used when possible to establish cervical fusion. Methyl methacrylate, alone or in combination with a bone graft, can be used to avoid problems associated with grafting in patients with metastatic disease. It also allows early postoperative ambulation without the need for cumbersome external immobilization devices. (27 refs)

- 79-0643** **Neoplastic Complications of Neurofibromatosis.** (Eng) Pantoja, E. (Dept. Radiology, USAF Medical Center, Wright-Patterson AFB, OH, 45433); Llobet, R. E.; Taveras, J. E. *Cutis* 22(6): 677-680; 1978.

Neurofibromatosis associated with secondary neoplasms is discussed. Some of the tumors that occur in neurofibromatosis are histologically benign; the most common being gliomas and meningiomas of the CNS. Other tumors of neurogenic derivation found in this condition include neurosarcoma, pheochromocytoma, and medullary carcinoma of the thyroid. The association between neurofibromatosis and cutaneous malignancies, carcinoma of the colon, leukemia, Wilms' tumor, and cancer of the kidney is of doubtful significance. Neurosarcomas are generally considered to represent a malignant degeneration of neurofibromatous tissue. The earliest sign of sarcomatous degeneration is usually a sudden and rapid increase in the size of an old, previously quiescent neurofibroma. In doubtful cases, the diagnosis may be established by biopsy of a cutaneous lesion. The treatment of choice is either wide local excision or amputation, depending on the location and extent of the lesion. These tumors are highly radioresistant and the prognosis of peripheral neurosarcoma associated with neurofibromatosis is very poor unless the tumors are completely removed. Benign CNS tumors may be curable if amenable to complete resection. (15 refs)

- 79-0644** **X-Ray Findings in the Skull in Neurofibromatosis.** (Ger) Galanski, M. (Radiologisches Klinik d. WWU, 4400 Munster, W. Germany); Benz, G. *ROEFO* 129(6): 757-761; 1978.

The x-ray findings in the skull in neurofibromatosis are reviewed, and x-rays of briefly described cases are included. Several types of tumors (neurinoma, neurofibroma, meningioma, craniopharyngioma, and chiasma tumors) are associated with this disease. The differential diagnosis depends on detection of mesodermal dysplasia, changes secondary to blastomatous processes, macrocephalus, and intracranial calcifications. (40 refs)

- 79-0645** **Multiple Endocrine Neoplasia, Type 2b.** (Eng) Carney, J. A. (Dept. Surgical Pathology, Mayo

Clinic and Mayo Foundation, Rochester, MN, 55901); Sizemore, G. W.; Hayles, A. B. *Pathobiol Annu* 8: 105-153; 1978.

The historical development, inheritance, diagnosis, pathology, prognosis, and treatment of multiple endocrine neoplasia, type 2b (MEN 2b) are reviewed. Age and sex factors are discussed, and pathologic changes in various parts of the body are presented. The syndrome is characterized by medullary thyroid carcinoma (MTC), pheochromocytoma (PC), ganglioneuromatosis, and a variety of skeletal and connective tissue abnormalities. Total thyroidectomy is necessary once abnormal basal or stimulated plasma immunoreactive calcitonin concentrations have been demonstrated. Although the PC's are rarely malignant, they are potentially lethal because of their cardiovascular effects. Since adrenal involvement is usually bilateral, total bilateral adrenalectomy with excision of any extraadrenal paraganglioma is the surgical treatment. Parathyroid hyperplasia occurs rarely in the syndrome; its treatment should be limited to excision of enlarged parathyroid glands. Both sympathetic and parasympathetic nerves and ganglia exhibit hypertrophy, hyperplasia, and structural disorders, a group of changes designated ganglioneuromatosis. This may be largely responsible for the striking eye and oral findings (diffuse lip enlargement and apparent eversion of the eyelids) and also for some of the serious symptoms and complications of the syndrome, particularly those referable to the alimentary tract. Ganglioneuromatosis is also found in the salivary glands, pancreas, gallbladder, upper respiratory tract, and urinary bladder. Increased growth of long bones, ribs, and skull results in a marfanoid habitus; skeletal and joint abnormalities and increased laxity of ligaments are also present. Ninety cases of MEN 2b have been reported, and although follow-up information is incomplete, 27 patients are known to have died as a result of the syndrome. The direct causes of death were MTC (15 deaths), PC (10 deaths), and alimentary tract complications (2 deaths). An additional 21 patients have metastatic MTC. Patients having the appearance characteristic of MEN 2b should be evaluated for thyroïdal C-cell and adrenal medullary function. (90 refs)

79-0646 Adenoid Cystic Carcinoma (Cylindroma) in the Head and Neck. A Clinical Review of 82 Cases.

(Eng) Zielke-Temme, B. (Dept. Radiology, Universitätsklinik Munster, Munster, W. Germany); Wannenmacher, M. *Acta Radiol [Oncol]* (Stockh) 17(5): 407-413; 1978.

Clinical data on 82 patients (52 women, 30 men) treated between 1958 and 1976 for adenoid cystic carcinoma (ACC) of the head and neck are reviewed. ACC is a rare malignant tumor that grows slowly, and local recurrence and generalized disease may occur even after long symptom-free periods. Approx half of the 82 tumors were located in the intraoral mucous or minor salivary glands, mostly in the hard and soft palate. The age of the patients ranged from 15 to 81 yr (mean 55.4 yr), with 68% being in the fifth and sixth decades. Mean duration prior to treatment was 1.7 yr. (35 refs)

79-0647 The Comparative Epidemiology of Selected Neoplasms Between Dogs, Cats, and Humans.

A Review. (Eng) Hayes, H. M. (Environmental Epidemiology Branch, NCI, 3C07 Landow Building, Bethesda, MD, 20014). *Eur J Cancer* 14(12): 1299-1308; 1978.

The epidemiologic features of tumors at nine different sites in dogs and cats are reviewed and compared with those of the corresponding human tumors whenever possible. Testicular neoplasms are the leading cause of cancer death in US men 25-29 yr old and the second in hospital prevalence in the dog. The primary difference between these tumors in men and dogs concern the incidence of certain cell types. The pathogenesis of spontaneous ovarian tumors in women and animals is obscure, but the similarity of the disease in women and dogs appears to make the latter a suitable model for testing suspected ovarian carcinogens. The ratio of female to male dogs with mammary gland tumors is about the same as the ratio in humans, and the distribution of the cancer by age in bitch dogs appears similar to that in women. There is also marked similarity in the epidemiological features of cancer of the kidney, urinary bladder, thyroid gland, chemoreceptor system (the glomus jugulare, glomus pulmonale, aortic body, and carotid body), brain, and blood-lymphatic system in humans and dogs. There is little information on cancer in cats, but what is available also shows a marked similarity to that on human cancers. (100 refs)

79-0648 Epidemiology of Malignant Tumors in Occupational Groups: Methods and Peculiarities of Study.

(Eng) Smulevich, V. B. (Oncological Scientific Center, USSR Acad. Medical Sciences, Kashirskoye shosse 6, 115478 Moscow, USSR); Bulbulian, M. A.; Katsnelson, B. A. *J Occup Med* 21(1): 11-14; 1979.

Research methods and problems encountered in epidemiological studies of occupational cancer are reviewed. In order to define certain malignant tumors as occupational, it is necessary to prove by epidemiological methods that a given form of cancer is observed in workers in specific industries significantly more often than in control groups. The relatively small size of industrial groups makes it necessary to use various methodological devices to obtain valid data, such as calculation of morbidity and death rate indices on data obtained for a number of years and relating them to the total size of the contingent studied during the same period; calculation of data by person-year methods; and calculation of data by person-years under risk. Difficulties in studying the epidemiology of occupational cancer include the long latent period, changes of occupation, frequent absence of archival materials for the period studied, and absence of environmental data. The development of a tumor of a certain site at a younger age than in the control group and the leveling out of characteristic sex differences in tumor prevalence are epidemiological criteria of occupational carcinogenesis. (16 refs)

79-0649 Geographical Variation in Cancer Incidence: A Clue to Causation. (Eng) Doll, R. (Dept. Regius Professor Medicine, Univ. Oxford, Oxford, England). *World J Surg* 2(5): 595-602; 1978.

The geographical variation in the incidence of 16 different cancers is discussed with special reference to esophageal cancer. Areas of high and low incidence of each of these cancers are tabulated. Differences in diet may be one of the etiological factors underlying these variations. (28 refs)

79-0650 The New Peptide Hormones of the Gut and Their Clinical Significance. (Eng) Bloom, S. R. (Dept. Medicine, Histochemistry, Royal Postgraduate Medical Sch. Hammersmith Hosp., DuCane Road, London W12 OHS, England); Polak, J. M. *Acta Gastroenterol Belg* 41(7/8): 371-393; 1978.

The gut endocrine system and the new peptide hormones of the gut are discussed in relation to their clinical significance.

Eight peptide hormones have their major biological actions through the circulation: gastrin is released from the stomach; pancreatic polypeptide is released from the pancreas; cholecystokinin, secretin, motilin, and gastrin inhibitory peptide are released from the upper small intestine; and neurotensin and enteroglucagon are released from the lower small intestine. These hormones are released in a characteristic way after a meal and the pattern is altered in a diagnostic manner by alimentary disease. The best recognized gut hormone disease occurs as a result of endocrine tumors. Hormonal peptides may be released only locally from an endocrine cell or they may be produced by and released from a neuron to have a brief local action. It has been proposed that the endocrine system is an out-pouching of the brain. The occurrence of several hormonal peptides (vasoactive intestinal peptide, somatostatin, substance P, enkephalin, bombesin, neurotensin, and gastrin/cholecystokinin) in both the gut and brain - where they may act as neurotransmitters - supports this concept. A better understanding of alimentary control systems should allow better insight into the etiology of human gut diseases. (13 refs)

CHEMICAL CARCINOGENESIS

79-0651 Mutagenic Analysis as a Means of Detecting Carcinogens in Foods. (Eng) Commoner, B. (Center Biology Natural Systems, Washington Univ., Box 1126, St. Louis, MO, 63130); Vithayathil, A.; Dolara, P. *J Food Protection* 41(12): 996-1003; 1978.

The possible origin of the mutagens that occur in commercial beef extract and in commercial foods containing beef extract was investigated. These mutagens were first identified in the nutrients used to culture the *Salmonella* for the Ames bacterial mutagenicity assay, and they require activation by the microsomal mixed-function oxidase system. The mutagens were not found in uncooked beef tissue or in beef stock. However, they were formed when beef stock was boiled extensively to produce beef extract. The same mutagens (as evidenced by their chromatographic behavior) were found when ground beef hamburgers were cooked at temperatures > 150-200 C. Well-done hamburgers cooked on an electric frying pan or hot plate or in an electric hamburger cooker (cooking temperatures 190-300 C) contained the mutagens. Hamburgers cooked under the heating element of an electric broiler or in a microwave oven (but not on the "browning tray") contained no significant mutagenic activity. Mutagen content increased with cooking time and was concentrated in the outer surface of the cooked hamburgers. These results show that mutagens found in beef extract and in cooked hamburgers represent a possible risk of unknown magnitude to persons ingesting them. However, the nutritional benefits of hamburgers can be enjoyed without incurring this risk, by a suitable choice of cooking methods. (15 refs)

79-0652 Monitoring and Risk Assessment by Means of Alkyl Groups in Hemoglobin in Persons Occupationally Exposed to Ethylene Oxide. (Eng) Calleman, C. J. (Dept. Radiology, Wallenberg Lab., Univ. Stockholm, S-106 91 Stockholm, Sweden); Ehrenberg, L.; Jansson, B.; Osterman-Golkar, S.; Segerback, D.; Svensson, K.; Wachtmeister, C. A. *J Environ Pathol Toxicol* 2(2): 427-442; 1978.

The degree of alkylation of histidine residues in Hb from blood samples collected from employees of sterilization plants using ethylene oxide (EtO) was determined. The max daily level of exposure was estimated to be 75 to 380 ppm/hr, depending on working site within the factory. Quantitative determination of N-3-(2-hydroxyethyl)histidine by mass fragmentography and ion-exchange amino acid analysis gave consistent results. Chronic exposure for > 18 wk (the lifetime of 1 RBC) would result in a steady-state degree of Hb alkylation nine times the weekly increment in the degree of alkylation. There was an acceptable agreement between the genetic risk estimate per unit dose and the one expected from mouse

data, the value for the EtO being approx 10 mrad-equivalents (ppm/hr)⁻¹. Because of its low mol wt, solubility in water and lipids, and rapid distribution to all parts of the body, it is likely that EtO induces a spectrum of cancers similar to that observed following whole-body exposure to penetrating low-linear energy transfer (low-LET) radiation. Although the finding of a cluster of two leukemia cases in one sterilization plant was statistically significant, it was not proof of the carcinogenicity of EtO. The dose of EtO corresponding to the limit of occupational risk to low-LET radiation would be 10 ppm/hr/wk, corresponding to an av concentration of 0.25 ppm. (35 refs)

79-0653 Multifocal Epithelioma in a Case of Psoriasis Treated with an Arsenical. (Pol) Frezer, O. (Klinika Dermatologii, Instytut Chorob Ulkadu Nerwowego i Narzadow Zmyslow AM, ul. Przybyszewskiego 49, 60-355 Poznan, Poland). *Przegl Dermatol* 65(6): 683-685; 1978.

A 70-yr-old man treated for 4 yr with potassium arsenite soln for psoriasis developed a multifocal basal cell epithelioma 12 yr after treatment. (8 refs)

79-0654 A Simple Method of Arsenic Speciation. (Eng) Brown, E. J. (Inst. Marine Science, Univ. Alaska, Fairbanks, AK, 99701); Button, D. K. *Bull Environ Contam Toxicol* 21(1/2): 37-42; 1979.

Low concentrations of As(V) can easily and routinely be separated from As(III) in water, soil, sediment, and biological samples using procedures similar to those for phosphate detection. The procedures are based on the fact that arsenate forms on alcohol-extractable molybdate complex but arsenite does not. Once separated, total As(III) or As(V) can then be determined by atomic absorption or distillation, allowing As speciation at part-per-billion levels. (15 refs)

79-0655 X-Ray Microanalysis of Asbestos in Tissue Culture Cells (Meeting Abstract). (Eng) Kindig, O. R. (Dept. Cell Biology, Tokyo Medical Dental Univ., Tokyo, Japan); Mizuhira, V. *J Electron Microsc (Tokyo)* 27(4): 379; 1978. (no refs)

79-0656 Cyclic Nucleotide Concentrations in Asbestos-induced Peritoneal Mesotheliomas in Rats (Meeting Abstract). (Eng) Stevens, R. H. (Radiation Res.

Lab., Univ. Iowa, Iowa City, IA, 52242); Will, L. A.; Osborne, J. W.; Cole, D. A.; Donham, K. J. *Cell Tissue Kinet* 11(6): 689; 1978. (no refs)

- 79-0657 Asbestos Cement Dust Inhalation by Hamsters.** (Eng) Wehner, A. P. (Dept. Biology and Energy Systems, Battelle, Pacific Northwest Lab., Richland, WA, 99352); Dagle, G. E.; Cannon, W. C.; Buschbom, R. L. *Environ Res* 17(3): 367-389; 1978.

The biological effects of inhaled asbestos cement (AC) dust were determined in male Syrian golden hamsters exposed to AC aerosols (average fiber count, 5-120 fibers/cm³) at concentrations of about 1-10 µg/liter for 3 hr/day, 5 days/wk. AC treatment had no consistent or significant effects on body or lung wt or survival time. The only histologic changes related to AC dust exposure were in the lungs. Ferruginous bodies associated with alveolar macrophages were found distributed throughout the lung and occasionally aggregated in areas around respiratory bronchioles. The number of ferruginous bodies and macrophages in the exposed animals increased with aerosol concentration and exposure time. The incidence of ferruginous bodies did not decrease in animals that were withdrawn from AC dust exposure prior to sacrifice. The incidence of slight fibrosis increased with dose in animals treated with AC dust for 15 mo before sacrifice. No other lesions were clearly related to AC dust exposure, and there were no primary respiratory carcinomas or mesotheliomas. (20 refs)

- 79-0658 Directed Health Survey of Workers Exposed to Asbestos.** (Swe) Hedenberg, L. (Goteborgs stads forvaltningshalsovard, Anders Perssonsgaten 2, S-416 64 Goteborg, Sweden); Hermansson, L.; Liden, M. A.; Thiringer, G. *Lakartidningen* 78(45): 4151-4152; 1978.

A total of 197 men (aged 17-66 yr, av 45 yr) with occupational exposure to asbestos (mainly machine operators, repairmen, pipe-layers, and pipefitters) were subjected to chest x-ray and pulmonary function tests. Pleural plaques were detected as the only change in 41 workers, 24 of whom were smokers. All 41 had normal lung function tests. Asbestosis (pulmonary fibrosis and pleural plaques) were found in 8 workers: 4 of them (1 nonsmoker and 3 smokers) exhibited restrictive ventilatory impairment, while the 4 others (all smokers) had normal lung function. The chest x-ray was normal in 146 cases, x-ray changes due to unrelated causes were found in 2; 72 of these 148 men were smokers. No one under the age of 51 had pulmonary fibrosis, and no one under the age of 38 had pleural plaques. (no refs)

- 79-0659 Cytology of the Respiratory Tract in Asbestos Miners.** (Eng) Plamenac, P. (Inst. Pathology,

Medical Faculty, Univ. Sarajevo, Sarajevo, Yugoslavia); Nikulin, A.; Pikula, B.; Markovic, Z. *Acta Med Jugosl* 32(4): 297-309; 1978.

The sputum specimens of two groups of asbestos miners, 23 cigarette smokers and 16 nonsmokers, were analyzed cytologically. The age of the miners ranged from 21 to 41 yr (av 27), the length of their occupational exposure from 1 to 17 yr (av 8). All the miners had normal chest roentgenograms and showed no signs of acute or chronic respiratory or other organic disease. All specimens contained a considerable amount of polymorphonuclear WBC, and all showed abnormal columnar cell findings. Squamous metaplasia was present in 19 smokers (10 without atypia, 9 with atypia) and in 9 of the nonsmokers (5 without atypia, 4 with atypia). None of the samples contained asbestos or ferruginous bodies. Several of the smokers and nonsmokers had eosinophilia (9 and 5, respectively), siderophages (21 and 12), and respiratory mucus spirals (19 and 5). The difference between the two groups in the incidence of mucus spirals was the only one that was statistically significant. It is concluded that long-term asbestos exposure can produce extensive alterations in the bronchial epithelium. (40 refs)

- 79-0660 Asbestos Bodies in Sputum (Letter to Editor).** (Eng) Whitaker, D. (Hosp. & Univ. Pathology Services, Queen Elizabeth II Medical Centre, Nedlands, Western Australia, Australia). *Acta Cytol (Baltimore)* 22(6): 443-444; 1978.

The finding of asbestos bodies (AB) in the sputum as opposed to lung tissue is probably an indication of significant exposure and may identify a group at high risk of the development of pathologic lesions of the lung and/or pleura. Among 70 patients with AB in the sputum, 47 had lung lesions (12 malignant mesotheliomas, 4 lung cancers with asbestosis, 15 lung cancers without asbestosis, and 16 cases of asbestosis). The lesions were due to occupational exposure in 40 patients, 31 of whom worked in asbestos mines. (6 refs)

- 79-0661 Awkward Medicolegal Problems in Asbestos Workers.** (Eng) Robertson, A. J. (Royal Liverpool Hosp., Liverpool L7 8XN, England). *J R Soc Med* 71(12): 864; 1978.

Medicolegal problems concerning compensation cases for asbestos workers are summarized briefly. Adequate and thorough occupational histories (in view of the minimum 10- and 20-yr latent time for asbestosis and mesotheliomas respectively), and evidence of exposure to asbestos must be presented. Persons residing with asbestos workers are also subject to asbestos-related diseases. (6 refs)

79-0662 Analysis of Genome Integrity During Exposure of Cultured Mammalian Cells to Cadmium Chloride (Meeting Abstract). (Eng) Hildebrand, C. E. (Cellular and Molecular Biology Group, Los Alamos Scientific Lab., Univ. California, Los Alamos, NM, 87545); Walters, R. A. *Biophys J* 25(2, part 2): 229a; 1979. (no refs)

79-0663 Cadmium Toxicity in *Physarum polycephalum*: Alterations of Nucleolar Ultrastructure and RNA Synthesis (Meeting Abstract). (Eng) Sina, J. F. (Univ. Michigan, Ann Arbor, MI, 48104). *Diss Abstr Int B* 39(6): 2725-2726; 1978. (no refs)

79-0664 The Effects of Cadmium Upon the Immune System of Mice (Meeting Abstract). (Eng) Bozelka, B. E. (Univ. Wisconsin, Madison, WI, 53706). *Diss Abstr Int B* 39(6): 2747; 1978. (no refs)

79-0665 Determination of Chromium in Working Areas by Atomic Absorption Spectrophotometry. (Rum) Dumitru, R. (Institutul de Igiena si sanatate publica, Bucharest, Romania); Ivanescu, A. *Rev Ig (Ig)* 27(3): 281-284; 1978.

An atomic absorption spectrophotometric method for determining chromium in the air of work areas, for example, in electroplating shops, is described. Chromium is sampled on membrane filters. The sensitivity of the method is 0.04 µg/ml. (21 refs)

79-0666 Direct-acting Mutagens in Automobile Exhaust. (Eng) Wang, Y. Y. (Sch. Public Health, Univ. California, Berkeley, CA, 94720); Rappaport, S. M.; Sawyer, R. F.; Talcott, R. E.; Wei, E. T. *Cancer Lett* 5(1): 39-47; 1978.

Samples of airborne particulates collected from Buffalo, New York, in 1961-1963 were assayed for mutagenicity to *Salmonella typhimurium* strains TA98, TA100, and TA1537, with and without rat liver microsome activation. The particulates were mutagenic to all three strains and did not require activation. Direct-acting (D-A) mutagenicity in TA98 was significantly correlated to the lead content of the sample, suggesting that automobile emissions might be the primary source of D-A airborne mutagens. Exhaust samples from passenger cars and from an experimental single-cylinder gasoline engine were also D-A mutagens in TA98, TA100, and TA1537; dose-response relationships were observed up to 1 mg/plate. Several fuels (iso-octane, premium leaded gasoline, regular low-lead gasoline, diesel fuel, and JP-4) and unused motor oil were not mutagenic, but used motor oil contained D-A mutagens. These results indicate that vehicular emis-

sions may contain D-A mutagens that result from combustion. The strain specificity and the fact that the mutagens were D-A rules out unsubstituted polycyclic aromatic hydrocarbons (PAH), aromatic amines, alkyl nitrosamines, or aliphatic epoxides, peroxides and hydroperoxides. Nitro-substituted PAH, some of which are direct-acting mutagens in *S. typhimurium*, may be the compounds observed in this study. Preliminary results with 6-nitrobenzo(a)pyrene support this suggestion. (29 refs)

79-0667 Ultrastructural Findings in Nasal Mucosa of Nickel Workers (Meeting Abstract). (Eng) Reith, A. (Norsk Hydro's Inst. Cancer Res., Oslo, Norway); Boysen, M.; Torjussen, W.; Solberg, L. A. *Ann Clin Lab Sci* 8(6): 503; 1978. (no refs)

79-0668 Induction of Renal Cancers by Intrarenal Injection of Nickel Subsulfide in Rats (Meeting Abstract). (Eng) Sunderman, F. W. (Univ. Connecticut Sch. Medicine, Farmington, CT); Maenza, R. M.; Hopfer, S. M.; Mitchell, J. M.; Allpass, P. R.; Damjanov, I. *Ann Clin Lab Sci* 8(6): 502; 1978. (1 ref)

79-0669 Morphological Transformation of Syrian Hamster Fetal Cells Induced by Nickel Compounds (Meeting Abstract). (Eng) Costa, M. (Inst. Materials Science, Univ. Connecticut, Storrs, CT, 06268); Nye, J.; Sunderman, F. W. *Ann Clin Lab Sci* 8(6): 502; 1978. (no refs)

79-0670 Serum Ceruloplasmin Concentrations in Rats with Primary and Transplanted Sarcomas Induced by Nickel Subsulfide. (Eng) Sunderman, F. W. (Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, P.O. Box G, Farmington, CT, 06032); Trudeau, E. A.; Horak, E.; Mitchell, J. M.; Allpass, P. R. *Ann Clin Lab Sci* 9(1): 60-67; 1979.

To study the value of serum ceruloplasmin (CPN) as an indicator of tumor progression, serum CPN concentrations were measured by p-phenylenediamine oxidase assay in sera from 30 control male Fischer rats, 5 rats with primary sarcomas induced by im injections of nickel subsulfide (Ni₃S₂), and 12 rats that had received Ni₃S₂-induced sarcoma transplants (sc) up to 6 wk earlier. The av serum CPN concentration in control rats was 0.35 g/liter, a value not significantly different from that in rats with primary sarcomas (0.38 g/liter). However, the max CPN concentration in rats that had received tumor implants 31 to 34 days earlier was 1.6-fold higher than the concentration obtained before tumor transplant. The CPN concentration was increased only 1.03-fold 32 days after sc injection of the NaCl vehicle alone. The av

latent period until death and av tumor diameter at death were greater in rats given sc transplants (5.7 wk from time of transplant and 8.1 cm, respectively) than in rats with primary sarcomas (16.4 wk from appearance of palpable tumor and 5.7 cm, respectively). The development of hyperceruloplasminemia in rats with transplanted sarcomas but not in rats with primary sarcomas was attributed to the greatly enhanced growth rates of the transplanted neoplasms. (63 refs)

- 79-0671 Carcinoma of the Cervix after Treatment with Prednisone and Azathioprine for Chronic Active Hepatitis.** (Eng) Norfleet, R. G. (Dept. Gastroenterology, Marshfield Medical Center, 1000 N. Oak Ave., Marshfield, WI, 54449); Sampson, C. E. *Am J Gastroenterol* 70(4): 383-384; 1978.

The case of a 24-yr-old woman who developed carcinoma of the cervix, in situ, after receiving immunosuppressive therapy for chronic active hepatitis is presented. The patient had received a total dose of 1,000 g of azathioprine and of 250 g of prednisone during a 5.5-yr period. The possibility that these drugs caused the malignancy is discussed, and evidence that hepatitis may be associated with increased cervical cancer incidence is reviewed. (9 refs)

- 79-0672 Risks in Chromium and Nickel Exposure for Stainless Steel Welders (Meeting Abstract).** (Eng) Stern, R. M. (Danish Welding Inst., Glostrup, Denmark). *Ann Clin Lab Sci* 8(6): 501; 1978. (no refs)

- 79-0673 Test of O,O-Dimethyl-1-hydroxy-2,2,2-trichloroethylphosphonate (Trichlorfon) for Carcinogenic Activity in Syrian Golden Hamsters (*Mesocricetus auratus* Waterhouse) by Intraperitoneal Administration.** (Ger) Teichmann, B. (Zentralinstitut für Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany); Schmidt, A. *Arch Geschwulstforsch* 48(8): 718-721; 1978.

O,O-Dimethyl-1-hydroxy-2,2,2-trichloroethylphosphonate (TCP: Trichlorfon) was tested for carcinogenic activity following ip injection (20 mg/kg/wk) in male and female Syrian hamsters. The animals were treated for 90 wk, at which time the max total dose was 204 mg in the males and 206 mg in the females. The animals were observed for approx 10 more weeks, and animals that did not die spontaneously were killed at 100 wk after the beginning of treatment. The treated animals showed no significant difference in tumor incidence compared with controls, and this was true whether or not the animals were divided by sex. (7 refs)

- 79-0674 Sister Chromatid Exchange Frequencies in Cultured Human Cells Exposed to an Organophosphorus Insecticide: Dichlorvos.** (Eng) Nicholas, A. H. (Div. Human Genetics, Dept. Human Biology, Univ. Leuven, Minderbroedersstraat 12, B-3000 Leuven, Belgium); Vienne, M.; Van Den Berghe, H. *Toxicol Lett* 2(5): 271-275; 1978.

The frequency of sister chromatid exchanges (SCE's) was examined in human cells grown in the presence of bromodeoxyuridine and exposed for 72 hr to 2.5, 5, or 10 µg/ml dichlorvos (DDVP). In human lymphocytes, there was a dose-dependent decrease in SCE frequencies with increasing DDVP concentrations. Because there was evidence that dimethyl sulfoxide, used as a solvent for DDVP, might be responsible for these results, an experiment in which no solvent was used was carried out. Again, a decrease in SCE frequency with increasing DDVP concentration was apparent, although this decrease was not statistically significant. In human fetal fibroblasts, however, there was an increase in the number of SCE's with increasing DDVP concentration. Although the differences in the response of fibroblasts and lymphocytes to DDVP were statistically significant ($0.05 > p > 0.01$), they were insufficient to be of biological significance. (15 refs)

- 79-0675 A Technique for the Measurement of Breakage and Repair of DNA Alkylated In Vivo.** (Eng) Eastman, A. (Dept. Biochemistry, Univ. Vermont Coll. Medicine, Burlington, VT, 05405); Bresnick, E. *Chem Biol Interact* 23(3): 369-377; 1978.

To assess the level of DNA damage induced in the livers and lungs of A/J and C57BL/6J mice after administration of the alkylating agent methylmethanesulfonate (MMS), the squash alkaline elution technique has been modified. At 4 hr after ip administration of MMS (120 mg/kg), damage to DNA (labeled in a series of 7 sc injections of 25 µCi (³H)thymidine (50 Ci/mM) that produced a specific activity of approx 500 disintegrations/min/µg liver or lung DNA) was readily demonstrable. This damage was repaired in the liver by 24 hr. The lung, particularly in the A/J mice, exhibited an increased alkaline elution rate when compared with C57BL/6J mice, and repair was not entirely complete by 24 hr based on the rate of alkaline elution of DNA. The rate of elution was dependent upon temperature: as the temperature was varied from 15 to 25 C, the initial elution rate (% DNA/hr) went from 1.50 to 6.90 in lung, and from 0.25 to 2.13 in liver. It is hoped that this modification will have much utility in the investigation of DNA repair in vivo. (18 refs)

- 79-0676 Reactions of Bisulfite, an Environmental Chemical, with Nucleic Acids and Other Biological Substances.** (Eng) Hayatsu, H. (Faculty Pharmaceutical Sciences, Univ. Tokyo, Bunkyo-ku, Tokyo 113, Japan). *Pure Appl Chem* 50(9/10): 1063-1068; 1978.

Bisulfite (BS) + semicarbazide, hydrazine, hydroxylamine, or methoxyamine inactivated and induced mutations in bacteriophage λ , and the action of BS + each amine was synergistic. These phenomena are probably due to chemical modifications of phage DNA. The rapid inactivation of phage by BS in air was O₂-dependent and was the result of damages to coat proteins of the phage caused by the free radicals generated from BS and O₂. (29 refs)

- 79-0677 Quantitative Analyses of Radiation- and Chemical-induced Lethality and Mutagenesis in Chinese Hamster Ovary Cells.** (Eng) Hsie, A. W. (Biology Div., Univ. Tennessee, Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, TN, 37830); O'Neill, J. P.; Couch, D. B.; SanSebastian, J. R.; Brimer, P. A.; Machanoff, R.; Fuscoe, J. C.; Riddle, J. C.; Li, A. P.; Forbes, N. L.; Hsie, M. H. *Radiat Res* 76(3): 471-492; 1978.

A Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) mutational assay was developed as a method for inducing and selecting 6-thioguanine (TG)-resistant mutants that are affected almost exclusively at the HGPRT locus. Ethyl methanesulfonate was used to illustrate the concentration-dependent interrelationships of cellular lethality and induced mutation and to study the structure-activity relationships of alkylating agents and heterocyclic nitrogen mustards. With all chemical mutagens studied, mutation induction increased linearly as a function of concentration with an apparent threshold effect. The mutagenicity of 79 physical and chemical agents, 42 of which were known to be carcinogenic or noncarcinogenic, was tested. Of 42 compounds with reported carcinogenicity in animal tests, 40 were mutagenic in the CHO/HGTRP assay. Fluorescent white, black, and blue lights were weakly lethal and mutagenic in the system; sun and sunlamp light were highly lethal and mutagenic; UV light induced mutations linearly from 2 to 27 J/m². The assay is recommended as a model system for studying the mechanisms of mammalian cell mutagenesis and as a short-term assay for screening environmental mutagens and carcinogens. (44 refs)

- 79-0678 Differential Sensitivity of DNA Replication and Repair in Permeable *Escherichia coli* Exposed to Various Monofunctional Methylating or Ethylating Agents.** (Eng) Hellermann, G. R. (Univ. Tennessee-Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, TN, 37830); Billen, D. *Chem Biol Interact* 23(3): 305-314; 1978.

The effects of various chemical alkylating agents on the replication and repair of DNA were investigated using *Escherichia coli* cells made permeable to deoxynucleoside triphosphates by brief treatment with toluene. Compounds employed included methyl methanesulfonate (MMS), ethyl methanesulfonates (EMS), N-methyl-N-nitrosourea (MNU), N-ethyl-N-nitrosourea (ENU), N-methyl-N'-nitro-N-ni-

trosoguanidine (MNNG), and N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG). Results revealed that replication of DNA was completely inhibited 10-15 min after exposure to MMS (5 mM or more), or MNU or MNNG (1 mM or more). Ethyl derivatives were less inhibitory than their methyl counterparts, with replication inhibition occurring in the following order: EMS < ENNG < ENU. Maximum replication inhibition occurred at a concentration of 20 mM or less for all compounds tested except EMS, which showed increasing activity up to the highest concentration tested (100 mM). Polymerase I (Pol I)-directed DNA repair synthesis (induced by x-irradiation) was reduced 40% by MNNG treatment (20 mM) and 30% by ENNG treatment (20 mM). ENU was slightly inhibitory to Pol I activity, while MMS, EMS, and MNU all resulted in slightly enhanced activity. It is concluded that DNA replication in this pseudo-in vivo bacterial system is very sensitive to the effects of known chemical mutagens, while DNA repair carried out by the Pol I repair enzyme is much less sensitive, and in some cases, unaffected. (16 refs)

- 79-0679 Carcinogenic Potential of Hycanthone in Mice and Hamsters.** (Eng) Bulay, O. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd St. and Dewey Ave., Omaha, NB, 68105); Urman, H.; Patil, K.; Clayson, D. B.; Shubik, P. *Int J Cancer* 23(1): 97-104; 1979.

The carcinogenicity of hycanthone was determined following ip or im injection in amounts up to the max tolerated dose (80 mg/kg/wk) into *Schistosoma mansoni*-infected and uninfected Syrian golden hamsters and Swiss mice. Hycanthone treatment did not affect the survival of the mice, although the survival of the infected hamsters was somewhat decreased due to an outbreak of "wet tail." No tumors attributable to treatment were observed in the hamsters, and the only tumors that increased in hycanthone-treated mice compared to controls were hepatomas and hepatocellular carcinomas (overall incidence 3.4% in infected controls, 10.6% in infected hycanthone-treated mice, 0.8% in uninfected controls, and 10.2% in uninfected hycanthone-treated mice). Statistical significance was attained only in the case of uninfected female mice injected ip and im with hycanthone, and then only at confidence levels of 92% and 95%, respectively. The results indicate that hycanthone is, at most, a very weak carcinogen for mouse liver and is inactive in hamsters. (30 refs)

- 79-0680 Microdetermination of Silicon in Blood, Serum, Urine, and Milk Using Furnace Atomic Absorption Spectrometry.** (Eng) Lo, D. B. (Dept. Pediatrics, Univ. Cincinnati Medical Center, Cincinnati, OH, 45267); Christian, G. D. *Microchem J* 23(4): 481-487; 1978.

A direct microanalytical method for the quantitative determination of silicon in human whole blood, serum, urine, and milk by furnace atomic absorption spectrometry is described.

The method combines atomic absorption analysis with the use of a heated graphite tube atomizer for the determination of silicon in microliter samples. The sensitivity is 1.3 nanograms. Silicon was found to be generally more concentrated in human blood than in serum by a factor of about 2. (16 refs)

- 79-0681 Inhibition of Azoxymethane-induced Intestinal Cancer by Disulfiram.** (Eng) Nigro, N. D. (Dept. Surgery, Wayne State Univ. Sch. Medicine, Detroit, MI, 48201); Campbell, R. L. *Cancer Lett* 5(2): 91-95; 1978.

A study was made of the effect of disulfiram (DS: 0.25% of diet) on intestinal tumor formation in intact and colostomized male Sprague-Dawley rats treated with azoxymethane (AOM: 8 mg/kg/wk for 24 wk, sc). The av numbers of small and large intestinal tumors per intact rat was significantly reduced by DS from 6.3 to 0.95. Furthermore, the number of rats developing tumors was reduced from 100% to 60%. In colostomized animals, DS reduced the number of tumors per rat from 5.0 to 0.13. There were no tumors in the small intestine and functional colon of these rats, and the number of tumors in the defunctionalized colon was reduced 25-fold. All tumors examined were adenocarcinomas. It appears that DS inhibits intestinal carcinogenesis with AOM by interrupting its metabolism to methylazoxymethanol and that this action is systemic. (7 refs)

- 79-0682 A Test of the Carcinogenicity of Enflurane, Isoflurane, Halothane, Methoxyflurane, and Nitrous Oxide in Mice.** (Eng) Eger, E. I. (Dept. Anesthesia, Univ. California, San Francisco, CA, 94143); White, A. E.; Brown, C. L.; Biava, C. G.; Corbett, T. H.; Stevens, W. C. *Anesth Analg (Cleve)* 57(6): 678-694; 1978.

The carcinogenic potential of enflurane, isoflurane, halothane, methoxyflurane, and nitrous oxide in air or in O₂ was tested in Swiss ICR mice. The mice were given 2-hr exposures to 1/32, 1/8, and/or 1/2 max allowable concentration (MAC) of the compounds both in utero (on gestation days 11, 13, 17, and 19) and after delivery (24 exposures at 2- to 3-day intervals beginning on postnatal day 5). In all, 1973 mice were sacrificed at 9 or 15 mo of age and examined for tumor development. Neoplastic lesions, mainly pulmonary adenomas, lymphomas, hepatocyte lesions, and liver vascular lesions, were found in all treatment and control groups, and although a few relationships of statistical significance were discovered in the large number of comparisons made, there was no consistent relationship noted with any anesthetic agent or dose. For example, male mice receiving 1/2 MAC isoflurane or 1/2 MAC halothane in air had a higher incidence of pulmonary adenomas and a significantly lower incidence of lymphomas than their air controls, but male mice given the same anesthetics and doses in an O₂ background did not differ from their O₂ controls. The results do not confirm the suggestion that isoflurane is a hepatocarcinogen and

they do not suggest that modern inhaled anesthetics pose a significant threat of carcinogenicity. (29 refs)

- 79-0683 Tissue-mediated Mutagenicity of Vinylidene Chloride in *Salmonella typhimurium* TA1535.** (Eng) Jones, B. K. (Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Cheshire, SK10 4TJ, England); Hathway, D. E. *Cancer Lett* 5(1): 1-6; 1978.

The Ames' mutagenicity assay, modified to assess the mutagenicity of gases and vapors, was used to assess the mutagenic potential of vinylidene chloride (VDC) when incubated with a fortified mammalian kidney or liver tissue postmitochondrial supernatant (S-9 mix) from various species. Seeded dishes of *Salmonella typhimurium* strain TA100 or TA1535 were exposed to an atmosphere of 5% VDC in air for 72 hr. TA100 and TA1535 gave similar results. VDC was strongly mutagenic when mediated by mouse kidney (23-fold increase in mutation frequency) and liver (18-fold increase) S-9 mix from Aroclor 1254 induced animals. VDC was weakly mutagenic when mediated by S-9 mix from uninduced mouse kidney (2.3-fold increase) and liver (1.6-fold increase). VDC was weakly positive (5-fold) when mediated by liver S-9 mix from similarly induced rats, but it was not mutagenic (≤ 1.2 -fold) when mediated by kidney or liver S-9 mix from noninduced rats. VDC showed weak mutagenicity (3-fold) when tested in a system mediated by liver S-9 mix from a human who had received long-term phenobarbital medication, but it was not mutagenic when mediated liver S-9 mix from noninduced marmosets or a noninduced human. Thus, the mutagenic potential of VDC depends considerably on the degree of activation of relevant drug-metabolizing enzymes. The results agree with the greater availability in treated mice than in rats of the reactive VDC metabolites 1,1-dichloroethylene oxide and chloroacetyl chloride and with the VDC carcinogenicity found in mice but not in rats. The data suggest that the limited number of primates examined respond more like rats than mice with regard to generation of alkylating metabolites and their reaction with bacterial DNA. (10 refs)

- 79-0684 Vinylchloride Sorption by Dry Casein Particles: Mechanistic Considerations.** (Eng) Biran, D. (Bait Yizzhak, Israel); Giacin, J. R.; Hayakawa, K.; Gilbert, S. G. *J Food Sci* 44(1): 59-61; 1978.

The amount of vinyl chloride monomer (VCM) sorbed by dry casein particles increases with a decrease in temperature or a reduction in moisture content of the particles. Adsorption is presumed to take place on the casein surface and to involve two distinctly different modes of sorption: active site sorption in which VCM molecules are attracted to the casein surface and an intermolecular attraction of VCM molecules, in which there is clustering around initially bound VCM. (10 refs)

- 79-0685 Study of Cocarcinogenic Effect of Polyvinyl Chloride and 20-Methylcholanthrene.** (Bul) Draganov, I. (Res. Inst. Oncology, Sofia, Bulgaria); Raichev, R.; Radeva, M. *Onkologiya* 15(3): 132-137; 1978.

The cocarcinogenic effect of polyvinyl chloride (PVC) and 20-methylcholanthrene (20-MC) was studied in random-bred rats. PVC plates were implanted in the animals and, 30 days later, the animals were inoculated with 20-MC (10 mg in 0.5 ml of sunflower oil, sc). The av latent period of tumor development was 2-5 mo, compared with 16-20 mo in animals exposed to PVC alone. The av latent period of tumor development in rats treated with 20-MC alone was also 2-5 mo. Tumor incidence was 17.5%-20% in rats exposed to PVC alone, 42% in rats treated with 20-MC alone, and 68% in rats exposed to PVC + 20-MC. (9 refs)

- 79-0686 Mutagenicity Studies with X-Ray-Contrast Media, Analgesics, Antipyretics, Antirheumatics and Some Other Pharmaceutical Drugs in Bacterial, Drosophila and Mammalian Test Systems.** (Eng) King, M. T. (Zentrallaboratorium für Mutagenitätsprüfung, Deutschen Forschungsgemeinschaft, Breisacher Strasse 33, Freiburg, W. Germany); Beikirch, H.; Eckhardt, K.; Gocke, E.; Wild, D. *Mutat Res* 66(1): 33-43; 1979.

Twenty-one frequently sold pharmaceuticals (6 organic x-ray-contrast media; 13 analgesics, antipyretics, and antirheumatics; 1 CNS stimulant; and 1 antidepressant), were tested for mutagenicity in several test systems. These consisted of the *Salmonella typhimurium* mutagenicity assay using strains TA1535, TA100, TA1538, TA98, and TA1537, each with and without liver homogenate activation; the *Escherichia coli* mutagenicity assay with and without liver homogenate activation, the host-mediated assay using *E. coli* and female NMRI mice; the sex-linked recessive lethal test in *Drosophila melanogaster*, and the micronucleus test with male and female NMRI mice. Four of the 21 compounds gave positive results: 1,2-dichloroethane in *Drosophila*, quinine dihydrochloride and dimethylaminophenazone in *S. typhimurium* TA98 in the presence of a liver homogenate derived from Aroclor-induced rats, and trilithium citrate in the micronucleus test. The apparent lack of correlation between the results obtained with these procedures cannot be explained, nor can the success or failure of the procedures be judged. However, the results do indicate an urgent need for further studies of the mutagenic effects of the four positive drugs. (36 refs)

- 79-0687 Role of Liver in the Development of Dysfunctional Diseases of the Mammary Gland in Rats.** (Rus) Ird, E. A. (Lab. Carcinogenic Agents, Cancer Res. Center, Moscow, USSR); Smirnova, I. O. *Biull Eksp Biol Med* 86(12): 713-715; 1978.

To evaluate the role of liver in the development of dysfunctional diseases of the mammary gland, random-bred female rats were subjected to sc injections with CCl₄ (0.01 ml/100 g, 2x/wk for 6 mo, with a 2-wk and a 3-wk interruption of treatment at 3 and at 8 wk, respectively after the initiation of the experiment). Animals were divided into four groups: Group 1 included 3.5- to 4-mo-old rats, Group 2 consisted of 12-mo-old rats, Group 3 included 3- to 4-wk-old rats with follicular cysts induced by constant lighting, and Group 4 consisted of 10- to 12-mo-old rats with permanent estrus. Contrary to the previously reported data on the increased incidence of mastopathy and mammary gland tumors after continuous exposure to CCl₄, the discrete administration of the hepatocarcinogen had marked preventive effect. In group 1, CCl₄ administration increased the latent period of mastopathy development from 7 mo (in controls) to 10 mo, and of mammary gland tumors (fibroadenomas) from 9.5 to 13 mo (the incidence of mastopathy and tumors in treated rats was 28% and 5%, respectively, compared with 26% and 5% in controls). Rats in Group 2 had significantly decreased incidence of mastopathy (37%, compared with 74% in controls), while the incidence of fibroadenomas was similar in treated and control animals (16%). In Group 3, CCl₄ administration resulted in a marked decrease in the incidence of follicular cysts (2%, compared with 81% in rats exposed to lighting alone and a significant decrease in the incidence of mastopathy (3% versus 74%) and of fibroadenomas (1% versus 11%). The minimal latent period of follicular cyst development increased from 1.5 mo in rats exposed to lighting alone to 9 mo in rats exposed to lighting and CCl₄. In Group 4, CCl₄ administration decreased the incidence of follicular ovarian cysts (55%, compared with 91% in controls) and of mastopathies (41% versus 91%), but did not affect the incidence of fibroadenomas (22% and 21%, respectively, in treated and control animals). These findings might indicate that the regression of CCl₄-induced cirrhosis can cause normalization of estrogen function. (10 refs)

- 79-0688 Carcinomas of the Liver in Osborne-Mendel Rats Ingesting DDT.** (Eng) Reuber, M. D. (NCI Frederick Cancer Res. Center, Frederick, MD, 21501). *Tumori* 64(6): 571-577; 1978.

DDT (1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane) carcinogenesis was studied in male and female Osborne-Mendel rats given 0-800 ppm DDT in corn oil and 600 or 800 ppm dry DDT in the feed for 2 yr. Rats given the higher doses of DDT developed tremors and experienced growth retardation. DDT at 400-800 ppm caused increased mortality in the females but did not affect mortality in the males. Liver size was increased in females given ≥ 200 ppm and in males given ≥ 400 . Hepatocellular carcinomas of the liver developed in 6/21 males (mostly in those given 800 ppm) and 3/12 females (given 200-600 ppm). Neoplastic nodules developed in the livers of four males, and a Kupffer cell sarcoma developed in one male. The first liver carcinomas appeared after 84 wk of DDT treatment. Other neoplasms included lung lym-

phosarcomas in 13 males, a lymphosarcoma of the spleen in 1 male, and carcinomas of the ovary in 11 females. (37 refs)

- 79-0689 Lack of Mutagenicity of Two Possible Metabolites of Halothane.** (Eng) Waskell, L. (Dept. Biochemistry, Univ. California, Berkeley, CA, 97420). *Anesthesiology* 50(1): 9-12; 1979.

Two probable halothane metabolites, 1,1-difluoro -2-bromo-2-chloroethylene and 1,1,1-trifluoro -2-chloroethane, were nonmutagenic in the Ames *Salmonella*/mammalian liver system. (18 refs)

- 79-0690 Oral Mucosal White Lesions Associated with Excessive Use of Listerine Mouthwash.** (Eng) Bernstein, M. L. (Dept. Oral Pathology/Pathology Sch. Dentistry, Univ. Kentucky Health Sciences Center, Louisville, KY, 40232). *Oral Surg* 46(6): 781-785; 1978.

Two cases are reported in which Listerine mouthwash induced white, diffuse lesions after prolonged surface contact. In one case, a 68-yr-old white man had filmy, translucent, white lesions affecting the lateral buccal and labial mucosa as well as the sulchi, crenulous ridges, and the floor of the mouth. A fissured pattern became apparent upon stretching, showing nonulcerated, linear, pink, parallel fissures interrupting the confluent white patches. In the second case, a 34-yr-old Indian man also showed diffuse, filmy, fissured or corrugated white lesions. The lesions could not be scraped off in either man, and they both admitted exorbitant use of Listerine. After discontinuing use of the mouthwash for 2 wk, the lesions disappeared in both cases. It appears that the changes were hyperkeratosis or acanthosis, resulting as a protective response to the low-grade chronic irritation, or coagulation of epithelial proteins as a result of the caustic exposure. The importance of this observation resides in the fact that the identification of these lesions allows separation from the idiopathic white lesions indicative of cancer. Moreover, if the aggravating constituent of the mouthwash is alcohol, this could have implications regarding the known role of alcohol as a cocarcinogen in oral cancer. (12 refs)

- 79-0691 Sorption of Vinylchloride by Selected Food Constituents.** (Eng) Biran, D. (Bait Yizhak, Israel); Gilbert, S. G.; Giacini, J. R. *J Food Sci* 44(1): 56-58; 1978.

The sorption of vinyl chloride monomer for selected food constituents (water, corn oil, oil-in-water emulsions, casein, and sucrose) was found to be affected significantly by the chemical nature of the food constituent, the initial concentration of VCM, and temperature. (12 refs)

- 79-0692 Ethylene Dibromide in Urban Air.** (Eng) Leinster, P. (Public Health and Water Resource Engineering Section, Imperial Coll. Science and Technology, London S.W.7, England); Perry, R.; Young, R. J. *Atmospheric Environment* 12(12): 2383-2387; 1978.

A procedure for the rapid sampling of ethylene dibromide, a potential carcinogen, in ambient air is described. Ambient levels in London air were in the range 0.001-0.17 $\mu\text{g}/\text{m}^3$, and levels on a garage forecourt were 1.2 and 1.8 $\mu\text{g}/\text{m}^3$. Ethylene dibromide was also measured in car exhaust, a calculation relating levels of organic lead to those of ethylene dibromide is presented. (9 refs)

- 79-0693 Simple and Rapid Determination of Epichlorohydrin at the Lower Parts per Billion Level by Gas Chromatography-Mass Fragmentography.** (Eng) Van Lierop, J. B. (Food Inspection Service, Nijenoord 6, Utrecht, Netherlands). *J Chromatogr* 166(2): 609-610; 1978.

A method for the determination of epichlorohydrin, based on gas chromatography-mass fragmentography, is described. The method is highly sensitive (to 6 ppb) and specific. (3 refs)

- 79-0694 The Influence of Contaminants on the Mutagenic Activity of Dibromochloropropane (DBCP).** (Eng) Biles, R. W. (Div. Environmental Toxicology, Dept. Preventive Medicine and Community Health, Univ. Texas Medical Branch, Galveston, TX, 77550); Connor, T. H.; Trieff, N. M.; Legator, M. S. *J Environ Pathol Toxicol* 2(2): 301-312; 1978.

The causative agent(s) and mechanism of mutagenic activity of technical grade (TG) 1,2-dibromo-3-chloropropane (DBCP) were investigated in the Ames mutagenesis test using *Salmonella typhimurium* TA1535. Without metabolite activation, TG DBCP was weakly mutagenic in the concentration range 50-1,000 $\mu\text{g}/\text{plate}$, whereas pure DBPC showed little or no mutagenicity in the same concentration range. Purification of the TG compound by distillation resulted in a first distillate with more than two-fold greater mutagenicity than the TG compound and a second distillate with mutagenicity similar to that of the TG compound. The first distillate was found to contain epichlorohydrin (ECH), which was present in the TG compound in an amount close to 1.5% by wt, as well as an unidentified compound. The second distillate contained smaller amounts of both compounds. The amount of ECH in the TG sample was calculated for each dose level tested, and the number of revertants obtained in tests of this sample could be attributed solely to the calculated amount of ECH in each test dose. Both TG and pure DBCP were strongly mutagenic in the concentration range 20-200 $\mu\text{g}/\text{plate}$ after S-9 metabolic activation. Results similar to those of the Ames test were obtained using a desiccator tech-

nique. The data indicate that in the direct in vitro evaluation, the mutagenicity of DBCP can be attributed almost entirely to the addition of the stabilizer ECH. (22 refs)

79-0695 Induction of Pulmonary Adenomas in Strain A Mice by Substituted Organohalides. (Eng)

Theiss, J. C. (Dept. Community Medicine, Sch. Medicine, Univ. California, La Jolla, CA, 92093); Shimkin, M. B.; Poirer, L. A. *Cancer Res* 39(2, Part 1): 391-395; 1979.

An investigation was made of the abilities of 28 organohalides (10 monochlorinated and 18 monobrominated derivatives of alcohols, esters, ethers, carboxylic acids, ketones, and amines that contained 2-4 carbon atoms) to induce lung adenomas in strain A mice. Groups of 20 mice (10 males, 10 females) received ip injections 3x/wk of either the max tolerated dose (MTD), 0.5 MTD, 0.25 MTD, or 0.20 MTD. Except for the more toxic compounds, 24 injections were given when possible. The mice were sacrificed 24 wk after the first injection and their lungs examined. 2-Chloro-N,N-dimethylethylamine hydrochloride, 3-chloropropionic acid, 4-chloro-1-butanol, and 2-bromoethanol produced an elevated pulmonary adenoma response that was significant by two different statistical tests. These substituted derivatives appeared to exert tumorigenic activity at lower doses than those of similar unsubstituted compounds (previous data); thus, nucleophilic substitution may increase the tumorigenicity of linear alkyl halides. Ethyl chloroacetate, 3-chloropropene, 3-chlorobutyric acid, 3-bromopropionic acid, and 3-bromopropylamine hydrobromide produced an elevated lung tumor response that was significant by only one of the statistical tests used. These compounds thus had borderline tumorigenicity in this bioassay. Four of the organochlorides and 15 of the organobromides showed no significant tumorigenicity. Among the negative compounds were three acylating agents, isobutyl bromide, butyl bromide, and benzoyl bromide. In general, the MTD's of the organobromides were substantially lower than those of the organochlorides. The finding that a greater percentage of the chloro compounds showed tumorigenicity than did the bromo derivatives was unexpected, based on chemical activity and on previous studies of mutagenicity and carcinogenicity among organohalides. The greater toxicity of the organobromides toward strain A mice may mask their potential tumorigenicity in some cases, as these compounds could not be administered in sufficient amounts to induce tumor formation. (14 refs)

79-0696 A Quantitative Dosing Schedule for the Induction of Transitional Cell Carcinomas in Female F344 Rats with the Use of N-Butyl-N-(4-hydroxybutyl)nitrosamine. (Eng) Becci, P. J. (Life Sciences Div., ITT Res. Inst., 10 W. 35th St., Chicago, IL, 60616); Thompson, H. J.; Grubbs, C. J.; Moon, R. C. *J Natl Cancer Inst* 62(1): 187-191; 1979.

The use of female rats avoids the complication of bladder stones, which are more frequent in males. Transitional cell carcinoma (TCC) of the urinary bladder was induced in female F344 rats by N-butyl-N-(4-hydroxybutyl)nitrosamine (OH-BBN), using a quantitative dosing schedule. Animals received 100, 150, or 200 mg OH-BBN by gastric intubation 2x/wk for 6 wk to a total dose of 1,200, 1,800, or 2,400, respectively, and they were sacrificed and examined for tumor growth at 6 and 12 mo after the first intubation. The diagnosis of TCC was determined by invasion of the underlying connective tissue or smooth muscle. Varying degrees of squamous and/or glandular metaplasia were observed in many of the TCC. Proliferative epithelial lesions included discrete hyperplastic lesions and noninvasive papillomas that did not meet the diagnostic criteria for carcinoma. At 6 mo, 20%, 60%, and 60% of the animals presented with TCC and 50%, 40%, and 40% exhibited discrete proliferative lesions with atypical epithelium (cellular atypia score $\geq +2$ on a scale of 0 to +5) at the respective doses. At 12 mo, the incidence of TCC was 90%, 80%, and 100% that of discrete proliferative lesions with atypical epithelium, 10%, 10%, and 13%, respectively. These data suggest that the lesions observed at 6 mo progressed to TCC by 1 yr and that the period of time after OH-BBN instillation rather than dose per se was the predominant factor in determining TCC incidence. Apparently, the two higher doses served only to reduce tumor latency and were in excess of the dose required to induce a high TCC incidence by 1 yr. (18 refs)

79-0697 Phenobarbital Stimulation of Cytochrome P-450 and Aminopyrine N-Demethylase in Hyperplastic Liver Nodules During DL-Ethionine Carcinogenesis. (Eng) Feo, F. (Cattedra di Patologia generale II dell'Universita Via Mancini, 1 Sassari, Italy); Canuto, R. A.; Garcea, R.; Brossa, O.; Caselli, G. C. *Cancer Lett* 5(1): 25-30; 1978.

The decrease of cytochrome P-450 (C/P-450) levels and aminopyrine N-demethylase (ADM) activity in hyperplastic nodules (HPN) and hepatomas induced by DL-ethionine, as associated with an impaired response to phenobarbital (PB) stimulation, was investigated. Male Wistar rats were fed a basal diet supplemented with 0.25% DL-ethionine for 5.5 mo, followed by basal diet only. At 7-9 mo after feeding initiation, some of the animals were injected ip with PB (80 mg/kg at 72 hr and 40 mg/kg at 48 and 24 hr before sacrifice). Liver tissue surrounding the nodules, HPN, and hepatomas were analyzed for amount of microsomal protein, C/P-450, and ADM. In rats not treated with PB, microsomes isolated from DL-ethionine-induced HPN and hepatomas had reduced C/P-450 levels and ADM activity compared with the organelles of control and surrounding liver. The values for the hepatoma were uniformly lower than those for the HPN. In addition, microsomal protein levels were 25%-28% higher in the HPN and 27%-30% lower in the hepatomas. PB administration increased the amount of microsomal protein, C/P-450, and ADM in all tissues tested. In the hepatomas,

the increase in C/P-450 and ADM per gram of tissue was very low and was compensated by a slight increase in microsomal protein. In HPN and in control and surrounding livers, C/P-450 and ADM increased more than microsomal protein, but the activity of PB was significantly lower in HPN than in control and surrounding livers. The inability of PB to greatly stimulate the monooxygenase system in HPN could be advantageous, in view of the fact that many carcinogens and hepatotoxic drugs are inducers of various constituents of this system. (21 refs)

- 79-0698 Concanavalin A Agglutination of Bladder Cells of Rats Treated with Bladder Carcinogens; A Rapid New Test to Detect Bladder Carcinogens.** (Eng) Karkizoe, T. (Urology Div., Natl. Cancer Center Hosp., Tokyo, Japan); Kawachi, T.; Okada, M. *Cancer Lett* 5(5): 285-290; 1978.

The agglutination by concanavalin A (Con A) of isolated bladder mucosa cells from male Wistar rats treated with N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN) or five of its analogs was investigated. Equimolar concentrations of the compounds were administered in drinking water for 1 wk, at which time animals were sacrificed and bladder mucosa cells isolated by treatment with EDTA and sonication. The agglutination assay was performed in a final volume of 40 μ l phosphate-buffered saline containing 2.5×10^6 cells/ml and 200 or 400 μ g/ml Con A, with or without 10 μ g/ml α -methyl mannoside. Cells treated with BBN (total dose 110 mg), N-butyl-N-(3-carboxypropyl)nitrosamine (115 mg), N-ethyl-N-(4-hydroxybutyl)nitrosamine (112 mg), and N-butyl-N-(2-hydroxyethyl)nitrosamine (115 mg) were positive, but cells treated with N-tert-butyl-N-(4-hydroxybutyl)nitrosamine (124 mg) and N-butyl-N-(3-hydroxypropyl)nitrosamine (101 mg) were negative. These results correlated well with the known carcinogenicity and mutagenicity of these compounds. Therefore, this method could provide a new rapid system for detecting potential bladder carcinogens. (22 refs)

- 79-0699 Aliphatic 3,4 Epoxyalcohols: Metabolism by Epoxide Hydrase and Mutagenic Activity.** (Eng) Ortiz de Montellano, P. R. (Dept. Pharmaceutical Chemistry, Sch. Pharmacy, Univ. California, San Francisco, CA, 94143); Boparai, A. S. *Biochim Biophys Acta* 544(3): 504-513; 1978.

The enzymatic hydrolysis of aliphatic epoxides bearing a vicinal hydroxyl group was investigated as part of a search for biologically significant intramolecular interactions of epoxides with other functional groups. Various substrates were incubated with rabbit hepatic microsomal suspensions equivalent to 1.0 g of intact liver for 30 min-2 hr under anaerobic conditions. Enzymatic hydrolysis of 1,2-epoxy-4-heptanol (I) gave a high yield of 1,2,4-heptanetriol. Both diastere-

omers of the substrate were hydrolyzed at comparable rates, since an equal mixture of the two was completely converted within 1 hr into an equal mixture of the two product diastereomers. Incubation of cis- or trans-3,4-epoxy-1-hexanol with liver microsomes yielded 1,3,4-hexanetriol, but at a relatively low rate. The trans isomer gave exclusively one diastereomer (erythro) of the triol, but the cis isomer gave the other diastereomer (threo). The product expected if a primary cationic intermediate were to be formed and trapped intramolecularly during the hydrolysis of Compound I, 2-propyl-4-tetrahydrofuranol, was not observed. A comparison of the mutagenic activity of 1-heptene, 1-hepten-4-ol, 1,2-epoxyheptane and I to *Salmonella typhimurium* TA100 revealed that only the latter is a detectable mutagen. Apparently, hydrogen bonding between the epoxide and the vicinal hydroxyl group does not interfere seriously with the hydrolytic mechanism of epoxide hydrazes, but it does enhance the bioalkylating potential of an otherwise unactivated aliphatic system. (31 refs)

- 79-0700 Alterations in *Bacillus subtilis* Transforming DNA Induced by β -Propiolactone and 1,3-Propane Sultone, Two Mutagenic and Carcinogenic Alkylating Agents.** (Eng) Kubinski, Z. O. (Div. Neurosurgery, Univ. Wisconsin, Madison, WI, 53706); Kubinski, H. *J Bacteriol* 136(3): 854-866; 1978.

The genetic properties of transforming DNA altered by either β -propiolactone (BPL) or 1,3-propane sultone (PS) treatment were studied. Transforming DNA from *Bacillus subtilis* was exposed to 50 mM BPL or PS and then used for transformation of competent bacteria to nutritional independence from tyrosine and tryptophan (linked markers) and leucine (an unlinked marker). The transforming ability of DNA was progressively lost during incubation with either chemical. For all three markers, the inactivation curve was biphasic, with a short period of rapid inactivation followed by one characterized by a much slower rate. The overall inactivation rate was different for all three markers and was presumably related to the size of the marker. The decrease in the transforming activity was in part due to the slower rate of penetration of alkylated DNA through the cellular membrane and its inability to enter the recipient bacteria. This decrease in the rate of cellular uptake, even for DNA eventually destined to enter the cell, began almost immediately after its exposure to the chemical and ultimately almost completely lacked recognition of the heavily alkylated DNA by the specific surface receptors of competent cells. Such DNA attached to sites on the surface of competent bacteria that were different from receptors specific for the untreated nucleic acid. This attachment was not followed by uptake of the altered DNA. The presence of albumin during the incubation with a carcinogen further increased the degree of inactivation, indicating that the artificial nucleoproteins produced under such conditions were less efficient in the transformation assay than was the naked DNA. Cotransformation of close markers progressively decreased, beginning immediately after the start of incubation of DNA with the chemicals. Extensively alkylated DNA

fractionated by sedimentation through sucrose density gradients showed a peculiar distribution of cotransforming activity for such markers; namely, molecules larger than the bulk of DNA ("megamolecules") showed less ability to transform the second marker than did some of the apparently smaller molecules that sedimented more slowly through the gradient. An increase in cotransformation of distant markers was evident in DNA molecules after a short exposure to an alkylating agent, but cotransformation of such markers did not occur in DNA treated for longer periods. The changes in the transforming and cotransforming activities of the alkylated DNA can be explained by knowledge of the physicochemistry of such DNA and in particular about the propensity of the alkylated and broken molecules to form complexes with themselves and with other macromolecules. (26 refs)

- 79-0701 Mutagenicity of Chlorinated Cyclopentadienes due to Metabolic Activation.** (Eng) Goggelman, W. (Dept. Toxicology, Gesellschaft für Strahlen-und-Umweltforschung, 8042 Munich-Neuherberg, W. Germany); Bonse, G.; Henschler, D.; Creim, H. *Biochem Pharmacol* 27(24): 2927-2929; 1978.

In an *Escherichia coli* K12 (343/113) mutagenicity test, the chlorinated cyclopentadienes tetrachlorocyclopentadiene and pentachlorocyclopentadiene were highly mutagenic after metabolic activation with mouse liver microsomes, whereas hexachlorocyclopentadiene (HCCP) was not. Metabolic insertion of oxygen into the C-1 position of HCCP is apparently hindered by the presence of two chlorine atoms, whereas no or only one chlorine atom at this position permits oxygen insertion. (15 refs)

- 79-0702 Comments on the Significance of Quasi-valence Number for Chemical Carcinogenesis.** (Eng) Lyle, R. E. (Dept. Chemistry, North Texas State Univ., Denton, TX, 76203); Lyle, G. G. *Experientia* 34(12): 1653-1654; 1978.

A number of examples are given to demonstrate that the quasi-valence number of a compound is not a useful criterion of carcinogenicity because it does not provide a structural screen capable of eliminating a large number of noncarcinogenic compounds while identifying most of the active ones. (3 refs)

- 79-0703 Short-Term Tests for Carcinogenesis. Evaluation, Predictive Values, Various Strategies.** (Fre) Bedouelle, H. (Laboratoire de Toxicologie genetique, Institut Pasteur, 28, rue du Docteur-Roux, 75015 Paris, France); Hofnung, M. *C R Acad Sci D (Paris)* 287: 891-894; 1978.

Statistical requirements for evaluating the Ames (*Salmonella typhimurium*) assay for testing carcinogens are discussed. Mathematical formulas of the relationship between evaluation of an agent by the Ames test and the predictive value of the test are presented. (7 refs)

- 79-0704 Screening for Carcinogens in the Working Environment.** (Dan) Olsen, J. (Smedebakken 10, 5270 Odense N., Denmark). *Ugeskr Laeger* 140(51): 3248-3249; 1978.

The value of Ames mutagenicity test in screening carcinogens in the working environment is discussed. Positive Ames tests have little predictive value, but it is highly probable that substances for which the test is negative are noncarcinogenic. (2 refs)

- 79-0705 Relation among Occupational Exposure to Potential Mutagenic/Carcinogenic Agents, Clinical Findings, and Bone Marrow Chromosomes in Acute Nonlymphocytic Leukemia.** (Eng) Mitelman, F. (Dept. Clinical Genetics, Univ. Hosp., S-221 85 Lund, Sweden); Brandt, L.; Nilsson, P. G. *Blood* 52(6): 1229-1237; 1978.

Chromosome findings in acute nonlymphocytic leukemia patients were correlated with occupational exposure to potentially leukemogenic chemicals. The chromosome banding pattern of bone marrow cells and clinical findings, including cytologic diagnosis, response to therapy, and survival time, were compared in two groups of adult ANLL patients: 23 occupationally exposed to chemical solvents, insecticides, and petroleum products and 33 with no history of occupational exposure to potential mutagenic/carcinogenic agents. As regards clinical findings, cases classified as acute myeloid leukemia were more common in the exposed group, whereas the monocytic varieties of ANLL were more common in the nonexposed group. Neither the complete remission rate nor the median survival differed significantly. In both groups, patients with only abnormal metaphases had poorer prognoses than those with normal bone marrow metaphases only. The detailed karyotypic findings showed striking differences between the two groups: (1) in the nonexposed group, only 24.2% had chromosome aberrations, whereas 82.6% of the exposed patients had aberrations; (2) in the exposed group, 84.2% of the patients with aberrations had at least one of four particular changes--monosomy 5 or 7 or trisomy 8 or 21, but none of the nonexposed patients had monosomy 5 or trisomy 8, and only one patient had monosomy 7 and one had trisomy 21. None of the remaining aberrations seen in the nonexposed group were found in any of the exposed individuals. The results suggest that correlations might exist between leukemogenic agents, cytologic type of leukemia, and chromosome progression of the leukemic cells. (28 refs)

- 79-0706 Carcinogenicity of Kepone.** (Eng) Reuber, M. D. (NCI Frederick Cancer Res. Center, Frederick, MD, 21501). *J Toxicol Environ Health* 4(5/6): 895-911; 1978.

Five studies of the carcinogenicity of Kepone (chlordecone, or decachlorooctahydro -1,3,4- metheno-2H-cyclobuta(cd)pentalen-2-one) are reviewed. Examination of histological sections indicated that Kepone is carcinogenic in both rats and mice. In one study, it induced malignant tumors in the liver of rats and mice and in another study in the liver of rats. Malignant tumors were also found in other organs in high-dose male and female rats and in low-dose male rats. The tumors were related to the dose of Kepone ingested, with females being more susceptible than males. There were also toxic changes following Kepone ingestion, particularly in male rats. These changes (interstitial fibrosis of kidney, polyarteritis, atrophy of testes) generally interfered with health of the rats and with tumor development. In mice, males were somewhat more susceptible to the carcinogenic effects of Kepone than females. Histopathological findings in dogs fed Kepone (25 ppm) for up to 128 wk included necrosis around central veins in the liver, focal hyperplasia of the liver, thyroiditis, hyperplasia of the thyroid, and foci of atypical cells in the ovary. No conclusions can be drawn from this study, but changes in the liver, thyroid, and ovary probably would have progressed if Kepone ingestion had been continued for at least 6 yr. (7 refs)

- 79-0707 Alteration of Human Cellular DNA by Neutral Red in the Presence of Visible Light.** (Eng) Speck, W. T. (Dept. Pediatrics, Case Western Reserve Univ., Cleveland, OH, 44106); Santella, R. M.; Brem, S.; Rosenkranz, H. S. *Mutat Res* 66(1): 95-98; 1979.

The combined effect of neutral red (NR: 3-amino-7-dimethylamino-2-methylphenazine hydrochloride) and visible light on the DNA of human (KB) cells growing in tissue culture was studied. KB cells were incubated for 1 hr at 37 C with or without 1 µg NR/ml. Some of the cultures were subsequently illuminated with white light for a total dose of 2 kilojoules (kJ)/m². DNA was analyzed on alkaline sucrose gradients. Incubation of the cell in the dark in the presence of 1 µg NR/ml or in the light without NR had no effect on the DNA sedimentation profile. Illumination with kJ/M² in the presence of NR had a profound effect on the sedimentation characteristics of the DNA. The NR-induced photodegradation of the DNA was prevented to a large extent when illumination was carried out in the presence of 1,4-diazabicyclo(2.2.2)octane (DABCO), a substance that quenches singlet oxygen. Incubation of cells in complete medium following illumination in the presence of NR resulted in DNA repair, as evidenced by a return of the DNA to the high-mol-wt region of the gradient. These findings indicate that illumination of cells in the presence of NR results in repairable structural changes in cellular DNA. The results with DABCO

suggest that the alteration of the cellular DNA results from singlet oxygen. (34 refs)

- 79-0708 Metabolism of Triphenylmethane Colors (III). Comparison of Tissue Distribution and Biliary Excretion for ³H-Benzyl Violet 4B and ³H-Fast Green FCF (Food Green No. 3) in Rats.** (Eng) Minegishi, K. (Natl. Inst. Hygienic Sciences, 18-1 Kamiyama 1-chome, Setagaya-ku, Tokyo, Japan); Morimoto, K.; Yamaha, T. *Shokuhin Eiseigakuzasshi* 19(5): 482-485; 1978.

The distribution and biliary excretion of ³H-labeled Benzyl Violet 4B (BV: reported carcinogen) and Fast Green FCF (FG: noncarcinogen) were compared in female Sprague-Dawley rats administered 10 micromoles/kg of each dye po. The levels of BV in the plasma, ear, abdominal skin, and abdominal muscle were higher than those of FG, and the cumulative amounts of BV and FG excreted in the bile were 4.26% and 3.81% of the dose by 24 hr, respectively. The biological half-lives of BV in plasma and other tissues were significantly longer than those of FG. (9 refs)

- 79-0709 Azo Reduction of Trypan Blue to a Known Carcinogen by a Cell-free Extract of a Human Intestinal Anaerobe.** (Eng) Hartman, C. P. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21501); Fulk, G. E.; Andrews, A. W. *Mutat Res* 58(2/3): 125-132; 1978.

A cell-free extract was prepared from *Fusobacterium* sp.2 and tested for its ability to reduce trypan blue. The incubation mixture contained 0.5 ml cell-free extract, 836 nanomoles of flavin mononucleotide (FMN), 33 micromoles of D-glucose-6-phosphate (Glc-6-P), 1 ml 0.1 M potassium phosphate buffer, and 2 micromoles of trypan blue. The inclusion of FMN and Glc-6-P was essential for max activity, but the presence of an exogenous NADPH generating system was not. Thin-layer chromatography and gas-liquid chromatography/mass spectroscopy showed that the product of trypan blue reduction by either the cell-free extract or sodium hydro-sulfite was o-tolidine, a known carcinogen. When this product and an equal amount of trypan blue were tested in the Ames' mutagenicity assay with *Salmonella typhimurium* strains TA1538 or TA98 in the presence of S-9 rat liver microsome mix, only the o-tolidine was mutagenic. It is suggested therefore that the teratogenic and oncogenic effects of trypan blue may be due to o-tolidine. (12 refs)

- 79-0710 A Case-Control Study of Hair Dye Use and Breast Cancer.** (Eng) Shore, R. E. (Inst. Environmental Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016); Pasternack, B. S.; Thiess-

en, E. U.; Sadow, M.; Forbes, R.; Albert, R. E. *J Natl Cancer Inst* 62(2): 277-283; 1979.

A case-control study of a possible association between hair dye use and subsequent development of breast cancer was made with the use of 129 breast cancer patients and 193 controls who had attended a multiphasic screening center between 1964 and 1976. All subjects were interviewed by telephone with regard to chronological time, duration, frequency, type, and color of hair dye used plus several risk factors associated with breast cancer. Incorporating the above use variables, measures of cumulative hair dye use at 0, 5, 10, and 15 yr prior to breast cancer development (or an equivalent time for controls) were determined. Confounding variables were controlled for by a multivariate risk factor score for each subject. The adjusted relative risks for breast cancer vs hair dye use always exceeded unity, but were generally not significant. After confounding variables were controlled, the integral measures (frequency x duration) were significantly related to breast cancer. Temporal pattern analysis showed that hair dye use ≥ 10 yr before cancer diagnosis was significantly related to the occurrence of the disease, suggesting that hair dyes act at some early stage of carcinogenesis and that the latency period is ≥ 10 yr. The strongest association occurred in women > 50 yr old and among those at low natural risk of breast cancer. The former finding is in keeping with recent concepts of possible divergent etiologies of pre- and postmenopausal breast cancer, and the latter suggests the hypothesis that high natural risk tends to mask the relatively small effects of hair dye exposure. (36 refs)

79-0711 Autoradiography of Deposition of Tobacco Smoke Particulate Matter in Isolated Perfused Rat Lung. (Eng) Bibby, M. C. (Postgraduate Sch. Studies in Medical and Surgical Sciences, Univ. Bradford, Bradford BD7 1DP, W. Yorkshire, England); Gilpin, C. J.; MacDonald, C. M.; Boardman, L. E. *Eur J Drug Metab Pharmacokin* 3(3): 141-145; 1978.

An isolated perfused rat lung system was used to study the deposition of tobacco smoke particulate material following inhalation of labeled mainstream smoke from standard flue-cured cigarettes. Radioactivity occurred throughout the lung but was concentrated within small bronchi. (12 refs)

79-0712 Cigarette Smoking and Bronchial Carcinoma: Dose and Time Relationships among Regular Smokers and Lifelong Non-Smokers. (Eng) Doll, R. (Radcliffe Infirmary, Univ. Oxford, Oxford, England); Peto, R. *J Epidemiol Commun Health* 32(4): 303-313; 1978.

In a 20-yr prospective study of the relationship between cigarette smoking and bronchial carcinoma in 34,440 British doctors, dose and time relationships were analyzed among regular smokers and lifelong nonsmokers. As is known, incidence

rates in the age range 40-79 are proportional to a power of duration of smoking, in excellent conformity with the predictions of the simple multistage model theory. To estimate this power, smoking duration was calculated by subtracting a chosen quantity (22.5 yr) from the age. Having done this, the best-fitting exponent was found to be 4.5 ± 0.3 ; ie, among cigarette smokers who started smoking at age 16-25 and who smoked ≤ 40 cigarettes/day, the annual lung cancer incidence in the age range 40-79 was $0.273 \times 10^{-12} \cdot (\text{cigarettes/day} + 6)^2 \times (\text{age} - 22.5)$ to the 4.5 power. The form of the dependence on dose in this relationship is subject not only to random error but also to serious systematic biases, which are discussed. However, there was certainly some statistically significant ($p < 0.01$) upward curvature of the dose-response relationship in the range 0-40 cigarettes/day, which is what might be expected if more than one of the stages (in the multistage genesis of bronchial carcinoma) was strongly affected by smoking. If a higher than linear dose-response relationship exists between dose per bronchial cell and age-specific risk per bronchial cell, this may help explain why bronchial carcinomas chiefly arise in the upper bronchi, as dilution effects might then protect the larger areas lower in the bronchial tree. (10 refs)

79-0713 The Chromatid Gap as a Folding Defect. Evidence from Mercaptoethanol and Caffeine Treatment (Meeting Abstract). (Eng) Brogger, A. (Genetics Lab., Norsk Hydro Inst. Cancer Res., Montebello, Oslo, Norway); Waksvik, H. *Clin Genet* 14(5): 282; 1978. (1 ref)

79-0714 Chromosomal Aberrations of Don Lung Cells of Chinese Hamster after Exposure to Vinblastine In Vitro. (Eng) Segawa, M. (Faculty Integrated Arts and Sciences, Hiroshima Univ., Hiroshima 730, Japan); Nadamitsu, S.; Kondo, K.; Yoshizaki, I. *Mutat Res* 66(1): 99-102; 1979.

Growing cultures of Chinese hamster (Don) lung cells were incubated with 0.0039, 0.0078, or 0.0156 $\mu\text{g/ml}$ vinblastine (VLB) for 2-32 hr, and the frequency of chromosome aberrations was determined. Colchicine (0.5 $\mu\text{g/ml}$) was added 2 hr before fixation. Chromosomes were stained with Giemsa, and 100 metaphase cells were examined for each VLB concentration. The number of lobulated nuclei at interphase increased gradually, beginning approx 2 hr after treatment. At all three concentrations, the numbers of chromosomal aberrations increased gradually up to 10 hr (when 28%, 44%, and 35% of metaphases contained aberrations at three increasing doses, respectively) and then decreased slightly. The mitotic index decreased steadily with increasing duration of treatment. The most common aberrations were gaps; chromatid and isochromatid breaks, rings, and chromatid exchanges plus other minor aberrations were also noted. Endoreduplicated chromosomes often contained multiple aberrations,

the incidence of which correlated with VLB concentration and duration of exposure. (15 refs)

79-0715 High-Performance Liquid Chromatography of Aflatoxins with Fluorescence Detection. (Eng)

Manabe, M. (Natl. Food Res. Inst., Ministry Agriculture and Forestry, Japan); Goto, T.; Matsuura, S. *Agric Biol Chem* 42(11): 2003-2007; 1978.

Studies were conducted to select various optimum conditions for the fluorometric determination of aflatoxin B₁, B₂, and G₂ by high-performance liquid chromatography using a 12 μ l flow cell. Good mutual separation of all four aflatoxins without quenching of their fluorescence was achieved using a silica gel column and a toluene-ethyl acetate-forming acid-methanol (89.0:7.5:2.0:1.5 v/v/v/v) solvent system. An increase in temperature from 20 to 35 C resulted in a 40% decrease in the fluorescence intensity of the aflatoxin B group, indicating the need for a relatively constant temperature when analyzing this group. The quantitative determinations of the four aflatoxins were linear in the range of 0.3-120 nanograms. Application of the method to samples of rice, corn, peanut meal, and mixed feed contaminated with aflatoxins showed that it was sensitive to levels as low as 10-20 ppb. (14 refs)

79-0716 A Method to Screen for Rubratoxin B and Other Mycotoxins in Corn. (Eng) Whidden, M. S. (Auburn Univ., Auburn, AL, 36830). *Diss Abstr Int B* 39(7): 3286B; 1979. (no refs)

79-0717 Mutagenicity and Antibacterial Activity of Mycotoxins Produced by *Penicillium islandicum* Sopp and *Penicillium rugulosum*. (Eng) Stark, A. A.

(Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Room 56-123, Cambridge, MA, 02139); Townsend, J. M.; Wogan, G. N.; Demain, A. L.; Manmade, A.; Ghosh, A. C. *J Environ Pathol Toxicol* 2(2): 313-324; 1978.

Twelve mycotoxins produced by *Penicillium islandicum* Sopp and *P. rugulosum* during solid-state fermentation on grains were purified and tested for mutagenicity and antibacterial activity in *Salmonella*/mammalian microsome assays. Lumiluteoskyrin, (+)rugulosin, rubroskyrin, and simatoxin induced mutations to 8-azaguanine resistance in suspensions of *Salmonella* strain TM677 (a histidine prototrophic revertant of strain TA1535 into which the ampicillin-resistance plasmid pKM101 was inserted), whereas (-)luteoskyrin, cyclochlorotine, iridoskyrin, pibasterol, chrysophanol, emodin, and skyrin were not mutagenic in this system. All *P. islandicum* mycotoxins except iridoskyrin, emodin, chrysophanol, and islandicin showed a concentration-dependent antibacterial activity. When tested with TM677 on plates, rubroskyrin and (+)rugulosin were antibacterial and mutagenic, simatoxin

in was mutagenic but only weakly antibacterial, and (-)luteoskyrin was antibacterial but not mutagenic. Purines and purine nucleosides protected TM677 cells from the inhibitory effects of 8-azaguanine. With a single exception, the mycotoxins did not induce histidine-independent revertants in *S. typhimurium* strains TA98 and TA100. A high concentration (130 μ g/reaction) of simatoxin had low mutagenic activity in suspensions of TA98. (20 refs)

79-0718 Dietary Protein Levels and Aflatoxin B₁ Metabolism in Rainbow Trout (*Salmo Gairdneri*). (Eng) Stott, W. T. (Dept. Food Science and Technology, Oregon State Univ., Corvallis, OR, 97331); Sinnhuber, R. O. *J Environ Pathol Toxicol* 2(2): 379-388; 1978.

The influence of three levels of dietary fish protein concentrate (FPC) on the in vitro activities of male rainbow trout hepatic enzyme systems that may be involved in the metabolism of aflatoxin B₁ (AFB) was studied. The size of the livers of fish given 52% and 62% FPC diets were increased compared with those of fish given a 32% FPC diet. Aldrin epoxidase was decreased twofold and 40%, respectively, in fish fed 52% and 62% FPC diets relative to the level in fish fed the 32% FPC diet. The activities of hepatic glutathione-S-epoxide transferase (20%), epoxide hydrolase (15%) and cytochrome c reductase (13%) also decreased with increasing dietary FPC. In contrast, a direct correlation was observed between increased FPC intake and cytochrome P-450 level and aflatoxicol production, with increases of 14% and 41%, respectively. The data provide evidence that the level of dietary protein can influence the in vitro activities of rainbow trout hepatic xenobiotic metabolizing enzyme systems. (54 refs)

79-0719 Distribution of (¹⁴C)-Labeled Aflatoxin B₁ in Mice. (Eng) Arora, R. G. (Dept. Pathology, Coll. Veterinary Medicine, Swedish Univ. Agricultural Sciences, S-750 07 Uppsala, Sweden); Appelgren, L. E.; Bergman, A. *Acta Pharmacol Toxicol (Kbh)* 43(4): 273-279; 1978.

The distribution of ¹⁴C-labeled aflatoxin B₁ (AFB) was studied in CBA mice by whole-body autoradiography. Six males and 2 nonpregnant and 2 pregnant females were given 3.13 μ Ci (7.8 μ g) AFB iv. The male mice were sacrificed 5, 20, and 60 min, 4 and 24 hr, and 4 days after injection. The nonpregnant females were sacrificed 5 and 60 min, the pregnant mice 20 min and 4 hr after injection, which in the latter was on gestation day 17. In addition to localization of AFB and/or its metabolites in the liver, bile, kidney, lung and urine, an uptake of ¹⁴C was also seen in the pigment of the Harderian gland and in the eye. A pronounced uptake was also seen in the pigment layer of the fetal eye and in the nasal mucosa but not in the fetal liver. A specific pattern of activity was seen in the adult kidney: there was a higher uptake of ¹⁴C in the medulla, leaving the cortex almost void of radioac-

tivity. This might indicate that the most vulnerable site of action of AFB is in the kidney. The significance of the specific kidney uptake and the pigment affinity of AFB are under further investigation. (14 refs)

- 79-0720 Variation in the Incidence of "Spontaneous" Tumours (Letter to Editor).** (Eng) Schoental, R. (Dept. Pathology, Royal Veterinary Coll., Univ. London, London, England). *Br J Cancer* 39(1): 101; 1978.

Carcinogenic mycotoxins (eg, T-2 toxin, aflatoxins) that can contaminate cereals harvested during wet and cold weather may have caused the drastic changes in the incidence of "spontaneous" tumors in laboratory animals at various institutes or at the same institute at different times. To avoid these misleading complications, the absence of mycotoxins from every batch of diet given to the animals must be ensured. (5 refs)

- 79-0721 Inhibition of Hepatic Toxicities from Polybrominated Biphenyls and Aflatoxin B₁ in Rats Fed Cauliflower.** (Eng) Stoewsand, G. S. (Dept. Food Service and Technology, Cornell Univ., Geneva, NY, 14456); Babish, J. B.; Wimberly, H. C. *J Environ Pathol Toxicol* 2(2): 399-406; 1978.

The effects of dietary cauliflower on the hepatotoxicity of polybrominated biphenyls (PBB's) and aflatoxin B₁ (AFB) were studied in weanling male Sprague-Dawley rats. In the first experiment, rats were fed a purified basal diet or a 25% freeze-dried cauliflower leaf diet for 3 wk, followed by 0, 1, or 50 ppm PBB in their respective diets for 20 days. In the second experiment, rats were fed the basal diet or a 20% cauliflower head diet plus 2 ppm AFB for 26 wk and then the basal diet for 15 wk. The 25% cauliflower leaf diet produced increased liver wts, especially in rats fed 50 ppm PBB. Hepatic aryl hydrocarbon hydroxylase (AHH) did not increase with the cauliflower diets but only with the highest level of dietary PBB. However, hepatic aminopyrene N-demethylase, p-nitroanisole O-demethylase, and cytochrome P-450 increased in a dose-dependent fashion in rats given cauliflower and PBB. (A preliminary study showed that freeze-dried cauliflower heads produced a similar pattern of hepatic mixed-function oxidase induction.) The apparent K_m of AHH in the liver, intestine, and kidney decreased, the V_{max} of intestinal AHH increased, and the V_{max} of renal AHH decreased in rats given cauliflower. Total lipids decreased in animals given cauliflower plus 50 ppm PBB. After 41 wk, rats given the basal diet and AFB died and showed Grades I and II liver adenomas, plus metastasis and severe internal hemorrhaging. All rats given cauliflower plus AFB lived, but they did exhibit lowered body wts and small, localized Grades I and II hepatic adenomas. Thus, microsomal enzyme induction, especially in liver and intestine, affords a detoxification mechanism for PBB and AFB in animals given dietary cauliflower. (25 refs)

- 79-0722 Alterations of Brain and Intestine Serotonin Levels in Hamsters Pretreated with Dietary Aflatoxin.** (Eng) Weekley, L. B. (Dept. Biology, Virginia Commonwealth Univ., Richmond, VA, 23284); Morgan, T. D.; Rea, F. W.; Kimbrough, T. D.; Llewellyn, G. C. *Cancer Lett* 5(2): 75-80; 1978.

The effects of dietary mixed-aflatoxin (AFT) pretreatment on serotonin levels were studied in male Syrian hamsters. Groups of six animals received either Purina laboratory meal (control diet) or a similar diet containing 30.3 ppm AFT (13.8 ppm AFB₁, 0.4 ppm AFB₂, 15.6 ppm AFG₁, and 0.5 ppm AFG₂) for 45 days, followed by the control diet for 123 days (recovery period). The animals were then sacrificed. Serotonin was decreased significantly in the duodenum of experimental animals, and although it was also decreased in brain, this difference was not significant. 5-Hydroxyindoleacetic acid was insignificantly elevated in AFT-treated animals. The livers of these animals displayed histopathological changes, including megalocytes, bile duct hyperplasia, and nuclear inclusion bodies. No gross tumors were seen in livers or intestines of any animal. Experimental animals experienced a net wt loss of 13.07% during the 45-day treatment period (vs control gains of 52.94%) and a rapid increase in the recovery period (87.95% vs 16.46%). However, the experimental animals never attained a body wt equal to that of controls. Following AFT treatment in the male hamster, responses to body wt, liver pathology, and serotonin appear to become "permanent" at differential levels. (21 refs)

- 79-0723 Morphology of Bacon and Its Possible Role in Formation of Nitrosamines.** (Eng) Cassens, R. G. (Muscle Biology Lab., Coll. Agricultural and Life Sciences, Univ. Wisconsin, Madison, WI, 53706); Ito, T.; Lee, M. *J Food Sci* 44(1): 306-307; 1978.

Morphologically, bacon is composed of regions of skeletal muscle or lipid-filled cells (adipocytes) characterized by a typical mammalian cell wall that encloses a single large lipid globule (LG). A thin layer of cytoplasmic protein, which contains cell organelles, is interposed between the cell wall and the LG. The interface between the nonpolar LG and the cytoplasmic and connective tissue proteins may present a unique site for reaction with nitrite-containing brine to form nitrosamines. (14 refs)

- 79-0724 The Dose-dependent Fate of 1,4-Dioxane in Rats.** (Eng) Young, J. D. (Toxicology Res. Lab., Dow Chemical Co., Midland, MI, 48640); Braun, W. H.; Gehring, P. J. *J Environ Pathol Toxicol* 2(2): 263-282; 1978.

A pharmacokinetic study was conducted to determine the dose-dependent fate of dioxane (given po, iv, and by inhalation) at doses identical to those given in toxic

cological studies in male Sprague-Dawley rats. The plasma concentration-time curves at low doses by each route were linear, with half-life values of about 1 hr. As the dose was increased above 10 mg/kg, the plasma clearance rate decreased, the fraction of the dose excreted in the urine as β -hydroxyethoxyacetic acid (HEAA) decreased, and the fraction of the dose excreted as dioxane in the urine and expired breath increased. The data could be described by a one-compartment open system model with parallel first-order (urinary and pulmonary excretion) and Michaelis-Menten (metabolism) type elimination kinetics. At saturation, the max velocity of the metabolism of dioxane to HEAA was about 18 mg/kg/hr. Multiple daily po doses of 1,000 mg/kg, but not 10 mg/kg, were excreted more rapidly than equivalent single doses, indicating that at high daily doses dioxane induced its own metabolism. The correlation of the dose-dependent fate of dioxane with the results of toxicological studies in rats supports the conclusion that there is an apparent threshold for the toxic effects of dioxane that coincides with saturation of the metabolic pathway for its detoxification. (26 refs)

79-0725 Residue Determination of Hydrazine in Water by Derivatization and Gas Chromatography.

(Eng) Selim, S. (Div. Chemistry and Physics, Food and Drug Admin., 200 C St., S.W., Washington, DC, 20204); Warner, C. R. *J Chromatogr* 166(12): 507-511; 1978.

A method is described in which the hydrazine residue in water is determined by converting hydrazine to acetone azine, extracting the acetone azine with methylene chloride, and detecting the acetone azine by gas chromatography using a nitrogen/phosphorus detector. The limit of detection is 0.1 ppb, and the recoveries averaged 92% for water fortified with 0.1-10 ppb hydrazine. The derivatization of trace hydrazine levels with a large excess of acetone proceeded quantitatively in 53 min in a methanolic system and in < 2 min in an aqueous system. (18 refs)

79-0726 Mechanism of Methylation of DNA Bases by Symmetric Dimethylhydrazine.

(Rus) Likhachev, A. Ia. (N. N. Petrov Res. Inst. Oncology, Leningrad, USSR); Petrov, A. S.; P'rvanova, L. G.; Pozharisskii, K. M. *Biull Eksp Biol Med* 86(12): 679-681; 1978.

The ability of disulfiram (DS) to block the formation of carbonium ion was employed for the analysis of the mechanism of methylation of DNA by 1,2-dimethylhydrazine (DMH). Random-bred rats received DS in sunflower oil (5 g/kg/d, po, for 8 days); 4 hr after the last DS administration rats were inoculated sc with ^3H -DMH (21 mg/kg) and 9 hr later were sacrificed. DNA specimens, extracted from the large intestine and the liver, were fractionated chromatographically. DNA from both intestine and liver lacked alkylated purines, but

in rats treated with DMH alone, the O⁶-methylguanine level in hepatic DNA was two times greater than in intestinal DNA. These findings confirm the hypothesis that the carcinogenic effect of alkylating agents is based upon the formation of O⁶-methylguanine. (14 refs)

79-0727 Intestinal Transit Time as an Important Factor in the Pathogenesis of Dimethylhydrazine-induced Rat Colon Cancer.

(Eng) Baker, A. R. (Surgery Branch, NCI, NIH, Bethesda, MD, 20014); Ward, J. M.; Simon, R. M.; Stinson, S. F.; Devereux, D. F. *Surg Forum* 29: 491-492; 1978.

Male Fischer 344 rats were given one of three rations ad libitum and weekly sc injections of dimethylhydrazine (DMH: 20 mg/kg). Rats fed the bulk-free elemental liquid ration had about a twofold prolongation in their intestinal transit time and, at 20 wk, developed larger and greater numbers of colon tumors than did rats fed solid, bulk-containing diets. Thus, intestinal transit time is important in the pathogenesis of DMH-induced rat colon tumors. (1 ref)

79-0728 1,2-Dimethylhydrazine-induced Methylation of DNA Bases in Various Rat Organs and the Effect of Pretreatment with Disulfiram.

(Eng) Swenberg, J. A. (Chemical Industry Inst. Toxicology, P.O. Box 12137, Research Triangle Park, NC, 27709); Cooper, H. K.; Bucheler, J.; Kleihues, P. *Cancer Res* 39(2, Part 1): 465-467; 1979.

The formation and persistence of methylated DNA bases following in vivo administration of ^{14}C -1,2-dimethylhydrazine (^{14}C -SDMH) with or without disulfiram (DS) pretreatment was studied in female BD-IX rats. The pretreatment group received 5 mg/g DS in their diet beginning 8 days prior to SDMH and continuing until sacrifice. All animals were inoculated sc with a single dose of 4 or 20 mg/kg SDMH and sacrificed 1.5 hr to 7 days later. The DNA of various organs was analyzed for the presence of methylated purines. The concentration of O⁶-methylguanine increased rapidly during the first 6 hr after SDMH administration and peaked at 12 hr, with the highest levels of N-7- and O⁶-methylguanine being detected in liver, followed by colon, ileum, and kidney. No purine alkylation was detected in stomach or brain. Removal of O⁶-methylguanine was most rapid in ileum and liver and least rapid in colon, the principal target for carcinogenesis. Rats receiving 20 mg/kg SDMH produced approx 10 times the amount of colonic O⁶-methylguanine produced in 4-mg/kg-treated rats. This is twice the level expected from a linear dose response. DS pretreatment reduced DNA alkylation to < 1% of that detected in rats receiving SDMH alone. The combination of persistent O⁶-methylguanine and cell replication, ie, DNA damage and repair, in the colon may provide an explanation for the organ-specific carcinogenicity of SDMH. (20 refs)

79-0729 Failure of Bran to Protect Against Experimental Colon Cancer in Rats. (Eng) Cruse, J. P. (Surgical Unit, University Coll. Hospital Medical Sch., Rayne Inst., University St., London WC1E 6FF, England); Lewin, M. R.; Clark, C. G. *Lancet* 2(8103): 1278-1280; 1978.

The effect of varying the fiber content of a diet on the induction of colon cancer by 1,2-dimethylhydrazine (DMH) was examined in a long-term study using 60 female Wistar rats. The rats were fed the same formula solid diet but given three different amounts of dietary fiber: 20 were given 4.8% wt/wt crude fiber, 20 were given 20% wt/wt bran, and 20 received no fiber. Half of the animals in each group were given DMH (40 mg/kg/wk sc) for 13 wk. All carcinogen-treated rats died during the 1-yr study, and all deaths were attributable to histologically proved adenocarcinoma of the colon. The incidence of colonic carcinoma in each DMH-treated fiber group was therefore 100%. These findings do not support the hypothesis that a high-bran diet will protect against chemically induced experimental colon cancer. (20 refs)

79-0730 Co-carcinogenic Effects of Dietary Cholesterol in Experimental Colon Cancer. (Eng) Cruse, J. P. (Surgical Unit, Univ. Coll. Hosp. Medical Sch., University St., London WC1, England); Lewin, M. R.; Ferulano, G. P.; Clark, C. G. *Nature* 276(5690): 822-825; 1978.

The ability of dietary cholesterol to promote the induction of colon cancer by dimethylhydrazine (DMH) was studied in female Wistar rats. DMH-treated (40 mg/kg/wk, sc, for 13 wk) animals fed Vivonex, a cholesterol-free, chemically defined liquid diet, showed a highly significant increase in both time to tumor presentation ($p < 0.001$) and survival ($p = 0.001$) when compared with carcinogen-injected controls fed a standard diet. This suggested that Vivonex protected against DMH carcinogenesis. The addition of cholesterol to Vivonex significantly reduced both the time to tumor presentation ($p < 0.001$) and survival ($p = 0.008$) and increased the incidence of metastases ($p = 0.028$). Sixty-seven percent of the animals fed Vivonex plus cholesterol had abdominal carcinomas at necropsy. The results suggested that cholesterol is a potent dietary cocarcinogen. (34 refs)

79-0731 Pathological Features of the Colonic Tumours Induced in Rats by the Administration of 1,2-Dimethylhydrazine. (Eng) Sunter, J. P. (Dept. Pathology, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, England); Appleton, D. R.; Wright, N. A.; Watson, A. J. *Virchows Arch [Cell Pathol]* 29(3): 211-223; 1978.

The frequency, distribution, and histopathology of colonic tumors induced in female Wistar Porton rats by 1,2-dimethylhydrazine (DMH, 15 mg/kg/wk sc for up to 30 wk) were studied. The incidence of colonic tumors was 92% in rats sacrificed at 24 wk, 89% in those sacrificed at 27 and 28 wk,

and 100% in those sacrificed at 30 wk. All tumors were of epithelial origin. Twenty-six percent of the tumors were benign adenomas, which arose in the distal three-fifths of the large bowel. Sixteen percent of the tumors were locally invasive, well-differentiated adenocarcinomas, which also arose in the distal three-fifths of the bowel. Well- and moderately well-differentiated adenocarcinomas showing greater invasion of the bowel wall were seen throughout the entire colon, especially the middle third, and they comprised 40% of the tumors. The largest tumors were poorly differentiated mucin-secreting adenocarcinomas that frequently invaded the full thickness of the bowel. They were largely confined to the proximal third of the colon and comprised 18% of all tumors. The proximal one-tenth of the colon was tumor-free. No completely anaplastic tumors were seen. The mean number of tumors per animal increased with duration of DMH treatment. Recently, demonstrated regional differences in the kinetic organization of normal colonic mucosa may influence the nature of the neoplastic change induced by DMH, thus accounting for the differences in tumor distribution. (14 refs)

79-0732 Tumours of the Anal Region Induced in Mice By 1,2-Dimethylhydrazine. (Eng) Turusov, V. S. (Cancer Res. Center, USSR Acad. Medical Sciences, Kashiirskoye Shosse 6, Moscow, 115478, USSR). *Cancer Lett* 5(2): 97-102; 1978.

When female CBA mice were treated with 1,2-dimethylhydrazine (8 mg/kg for 40 wk, sc), they developed, in addition to tumors of the uterus, colon, liver, and other sites, a high incidence of benign and malignant tumors in the anal region. There were 28 in all, 12 perianal gland tumors, 12 squamous carcinomas, and 4 papillomas and keratoacanthomas. The first five perianal tumors were found 22-30 wk after the start of treatment, and they appeared as small intracutaneous or sc nodules undergoing ulceration. The structure of these lesions was similar to that of the perianal sebaceous glands, and they were surrounded by a fibrous capsule. They largely retained their organoid structure; ie, a squamous component originating from the ducts and a sebaceous component. In advanced stages, one of these components (usually the squamous) dominated. Most of these tumors were well demarcated from the surrounding tissues. Morphologically, they could be diagnosed as adenomas, adenoacanthomas, or carcinomas. In at least 4/12 squamous cell carcinomas, a perianal gland origin was indicated by the presence of sebocytes within the tumors. The papillomas or keratoacanthomas were found at the junction of the cylindrical and squamous epithelium of the anus. This study showed that many DMH-induced anal tumors do not originate primarily from the epidermis but rather from the perianal glands located deep in the subcutis. (7 refs)

79-0733 Dietary Fibre and Chemically Induced Bowel Tumours (Letter to Editor). (Eng) Brown, S. M.

(Biometry Branch, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709); Falk, H. L. *Lancet* 2(8102): 1252; 1978.

A previous experiment demonstrating a dose-response influence of dietary fiber in protecting rats against the carcinogenic effects (bowel tumors) of dimethylhydrazine (DMH) could have been better designed. The protein and fat levels in the diets should have been held constant, the number of animals should have been larger, and the dose of DMH should have been varied. In addition, two diets used, which represented the extremes of fiber content, were growth inhibitory at a toxic level. (5 refs)

79-0734 Experimental Colonic Tumours in the Rat. III. Induction Time, Distribution and Appearance of Induced Tumours. (Eng) Lindstrom, C. G. (Res. Labs., Depts. Diagnostic Radiology and Pathology, Malmo Allmanna Sjukhus, S-214 01 Malmo, Sweden); Rosengren, J. E.; Ekberg, O. *Acta Radiol [Diagn] (Stockh)* 19(5): 799-816; 1978.

The induction time, distribution, and appearance of colonic tumors induced in Wistar/Furth and BD rats by 1,2-dimethylhydrazine (DMN, 20 mg 3x/wk ip for 11 wk, 15-25 mg/wk sc for 15 wk, or 15-45 mg/kg/wk sc for 4-12 wk) or N-methyl-N'-nitro-N-nitrosoguanidine (MNNG, 0.5 ml of a 0.25% soln 1x/wk for 11-16 wk intrarectally) were studied. A total of 214 malignant adenomatous colonic tumors developed in 114/189 drug-treated rats; 18 of these tumors were overlooked or misinterpreted at radiography. Induction time was shorter with DMH given sc in a small dose than with DMH given ip in a higher dose. DMH-treated rats most often developed one to two tumors, and adenocarcinomas of well, moderately, and poorly differentiated types occurred; 60% of these tumors appeared within 9 mo. MNNG-treated rats often developed more than three tumors, and the adenocarcinomas were mainly well differentiated; 78% of these tumors appeared after 9 mo. MNNG-induced tumors did not metastasize and did not occur outside the large bowel, whereas DMH-induced tumors metastasized ip and to lymph nodes in 21 (17.5%) cases and appeared outside the large bowel (small bowel, kidney, liver-biliary tract) in 64 cases. The distribution and occurrence of carcinomas and adenomas suggested that they are generated by the same biologic mechanism acting on the epithelium. There seemed to be a relationship between the various types of mucosa in the colon and rectum and the carcinomas developing from them. (24 refs)

79-0735 The Degradation of Different Forms of Cytochrome P-450 In Vivo by Fluroxene and Allyl-isopropylacetamide. (Eng) Bradshaw, J. J. (Dept. Medical Biochemistry, Univ. Cape Town Medical Sch., Cape Town, South Africa); Ziman, M. R.; Ivanetich, K. M. *Biochem Biophys Res Commun* 85(3): 859-866; 1978.

Fluroxene (FL) and allylisopropylacetamide (AIA) decreased hepatic cytochrome (cyt) P-450 levels in control rats and rats pretreated with phenobarbital (PB) or 3-methylcholanthrene (3-MC) and equivalently decreased microsomal heme, aniline binding, and p-nitroanisole demethylase. FL and AIA degraded multiple forms of cyt P-450 following PB induction, but degraded in the greatest amounts the form(s) of P-450 induced by PB. After 3-MC induction, FL preferentially degraded cyt P-448, but AIA remained relatively specific for the form(s) of P-450 induced by PB. (23 refs)

79-0736 Chemical Carcinogen FANFT Induces an Increase in Intramembrane Particle Numerical Densities in Urinary Bladder Epithelium (Meeting Abstract). (Eng) Pauli, B. U. (Dept. Pathology, Rush Medical Coll., Chicago, IL); Friedell, G.; Weinstein, R. S. *J Cell Biol* 79(2, part 2): 227a; 1978. (1 ref)

79-0737 Topography and Numerical Densities of Intramembrane Particles in Chemical Carcinogen-induced Urinary Bladder Carcinomas in Fischer Rats. (Eng) Pauli, B. U. (Dept. Pathology, Rush-Presbyterian-St. Luke's Medical Center, 1753 W. Congress Parkway, Chicago, IL, 60612); Friedell, G. H.; Weinstein, R. S. *Lab Invest* 39(6): 565-573; 1978.

Intramembrane particle (IMP) numerical densities and topographic distributions were compared in chemically induced noninvasive and invasive bladder tumors. Moderately well differentiated papillary transitional cell carcinomas were produced by feeding weanling male Fischer rats N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide (FANFT) at a dose of 0.2% of their diet for 26 wk. Tumors developing by 26 wk were small and noninvasive. At 61 wk, the tumors were large and invasive. The numbers of IMP on the protoplasmic (P) faces (IMPP) in both noninvasive and invasive urothelial tumors were significantly increased over control values ($p < 0.01$). The density of IMP particles on the external faces in normal rat urothelium and in noninvasive and invasive FANFT-induced bladder tumors were not significantly different. Using several statistical methods that test IMP topography vis-a-vis the Poisson (random) hypothesis, it was demonstrated that IMP are mathematically randomly distributed in the large majority of plasma membranes of cells in normal rat bladder epithelium and in invasive FANFT-induced tumors. In noninvasive carcinomas, IMP were in a lattice-like arrangement in half of the tumor cells and randomly distributed in the remainder. The results document that, in the course of malignant transformation of the rat urinary bladder epithelium, numerical densities and topographic distributions of IMPP are altered. Such alterations may be related to intrinsic or extrinsic stimuli that introduce changes in the interactions of the plasma membrane with membrane-associated constituents. The possibility also exists that changes in IMPP numerical densities and topographic

distributions with neoplastic transformation may represent epiphenomena, at least in FANFT-induced urinary bladder carcinomas in Fischer rats. (63 refs)

- 79-0738 Effect of Azathioprine and OK-432 on Urinary Bladder Carcinogenesis in Rats.** (Eng) Cohen, S. M. (First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan); Fukushima, S.; Tsuda, H.; Murasaki, G.; Ito, N. *Gann* 69(6): 773-779; 1978.

The effect of azathioprine (ATP) and OK-432 on bladder carcinogenesis in rats was evaluated using the carcinogens N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) and N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT). OK-432 is a streptococcal preparation that enhances cellular immune and reticuloendothelial responsiveness to tumors in animals and, in preliminary studies, in humans. Male Fischer rats were administered 0.01% BBN in the drinking water or 0.2% FANFT in the diet for 8 wk, alone, or before, during, or after 8 wk of 0.02% ATP in the diet. Some rats were given ATP alone, others a control diet. In another experiment, the rats were given 8 wk of BBN alone or before, during, or after 8 wk of OK-432 (5KE 2x/wk, sc). One group of rats received BBN for 8 wk followed by OK-432 for 32 wk. ATP did not affect FANFT bladder carcinogenesis in any treatment. When ATP was fed simultaneously with BBN, however, there was a significant increase in the incidence of bladder tumors, although ATP had no effect on tumor incidence when it was administered before or after BBN. Short-term administration of OK-432 before, during, or after BBN did not affect bladder carcinogenesis, but if OK-432 was begun after BBN and continued until the end of the experiment, the incidence of BBN-induced bladder tumors was significantly reduced. No bladder lesions were observed in control rats or in rats receiving ATP or OK-432 alone. (27 refs)

- 79-0739 The Effects of Dietary Protein, Fat and 2-Acetylaminofluorene on the Microsomal Activity Levels of Liver from BALB/c Mice.** (Eng) Lazear, E. J. (Dept. Health, Education and Welfare, Natl. Center Toxicological Res., Food and Drug Admin., Jefferson, AR, 72079); Louie, S. C.; Shaddock, J. G.; Barren, P. R.; Norvell, M. *Toxicol Lett* 2(6): 345-350; 1978.

The effects of dietary protein (12% or 24% of the diet), fat (4% or 24% of the diet, as corn oil), and 2-acetylaminofluorene (2-AAF, 0 or 500 ppm) on the biological activity of the hepatic microsomal system were studied using weanling female BALB/c mice and the Ames *Salmonella typhimurium* assay system. The experimental diets were fed continuously for 77 wk. In the Ames assay, liver S-9 fractions from animals on the high-fat diets had significantly lower activity levels than the fractions from animals on the low-fat diets. Protein concentration had no significant effect, but 2-AAF had a

strong inducing effect, especially in the high-fat diet groups. Thus, the metabolic functions of laboratory animals can be altered drastically by modifications in the diet. Nearly all of the animals given 2-AAF had liver nodules, and numerous sc growths were observed in the inguinal areas and the regions near the mammary glands. (7 refs)

- 79-0740 Effects of Selenium and Retinoic Acid on the Metabolism of N-Acetylaminofluorene and N-Hydroxyacetylaminofluorene.** (Eng) Daoud, A. H. (Dept. Biochemistry, Univ. Texas System Cancer Center, M.D. Anderson Hosp. Tumor Inst., Houston, TX, 77030); Griffin, A. C. *Cancer Lett* 5(4): 231-237; 1978.

The effect of selenium (4 ppm in drinking water for 3 days) or retinoic acid (RA: 0.25% wt/wt in the diet for 3 days) on enzymes involved in the metabolism of acetylaminofluorene-9-¹⁴C and N-hydroxyacetylaminofluorene-9-¹⁴C (AAF and OH-AAF: each, 17 mg/kg ip) and the binding of these two compounds to liver nucleic acids was studied in male Sprague-Dawley rats. Se and RA enhanced the liver activity of OH-AAF glucuronyl transferase, decreased the activity of sulfotransferase, and had no effect on AAF deacylase. Se-treated rats showed lower radioactivity in most liver fractions than controls after AAF and OH-AAF administration. The livers of rats given Se and AAF or OH-AAF did not differ markedly from control rats with respect to ethyl acetate- and ether-extractable components. However, the level of these components was 20 times lower in AAF-treated livers than in OH-AAF-treated livers. Se inhibited the binding of OH-AAF to liver DNA and transfer RNA by 30% and 20%, respectively, but had a negligible effect on the binding of AAF to liver DNA. The data support the hypothesis that retinoids and Se slow down or reduce chemical carcinogenesis by altering the metabolism and detoxification of cancer inducing agents. (14 refs)

- 79-0741 2-Acetylaminofluorene-induced Unscheduled DNA Synthesis in Hepatocytes Isolated from 3-Methylcholanthrene Treated Rats.** (Eng) Casciano, D. A. (Div. Mutagenesis Res., HFT-120, Natl. Center Toxicological Res., Jefferson, AR, 72079); Farr, J. A.; Oldham, J. W.; Cave, M. D. *Cancer Lett* 5(3): 173-178; 1978.

The induction of unscheduled DNA synthesis (UDS) by 2-acetylaminofluorene (AAF) and N-hydroxy-2-acetylaminofluorene (N-OH-AAF) in hepatocytes isolated from untreated or 3-methylcholanthrene-induced (3-MC: 100 mg/kg ip 24 hr before hepatocyte isolation) Sprague-Dawley rats was studied autoradiographically. A dose-dependent increase in UDS was noted after N-OH-AAF treatment even without 3-MC induction, suggesting that hepatic cells from uninduced animals retained sufficient enzymatic capacity to metabolically activate N-OH-AAF. All doses of AAF increased the level of

³H-thymidine incorporation above that of controls, but the increases were not dose-dependent. This suggests that cellular levels of N-hydroxylating enzymes were inadequate. Upon 3-MC treatment, however, the increase in AAF-induced UDS was dose-dependent. In both cases, 3-MC treatment not only increased the amount of UDS/cell, but also the percentage of cells induced to repair their DNA. These results confirm the observation that induction of UDS in primary rat hepatocyte cultures can be used to detect potential carcinogens, and they suggest that the sensitivity of the system may be enhanced (at least for aromatic amines) by 3-MC treatment prior to hepatocyte isolation. (11 refs)

79-0742 The Binding of ¹⁴C-Labelled Acetylaminofluorene to Nuclear Proteins and DNA. (Eng) Gro-now, M. (Cancer Res. Unit, Univ. York Heslington, York YO1 5DD, England); Lincoln, J. C. *Cancer Lett* 5(5): 269-275; 1978.

A study was made of the covalent binding of acetylaminofluorene (AAF) to liver nuclear protein fractions and DNA of male Wistar rats given two doses of ¹⁴C-labeled carcinogen (100 μ Ci, ip) 24 hr apart beginning 48 hr or 2 wk before sacrifice. Livers were removed immediately, nuclei were isolated, and most of the non-histone proteins (NHP) were removed by extraction with 8 M urea. After 48 hr, 80.9% of the AAF was bound to the urea extracted NHP, which also had the highest specific activity. Relatively small amounts were bound to histones (9.9%), residual proteins (5.9%), and DNA (3.3%). After 2 wk the label was redistributed, with more being present in histone and residual protein fractions, but again only a small amount of carcinogen was bound to DNA (0.23%). Pretreatment of rats with phenobarbital (PB: 1 mg/ml) or sodium sulfate (10 mg/ml) in drinking water for 10 days prior to AAF administration reduction binding to all fractions, with PB having a stronger effect. Contrary to expectation, PB did not produce higher binding to DNA. In fact, it reduced the specific activity of the DNA. Isoelectric focusing analysis of the NHP in polyacrylamide gels showed a complex binding pattern, with 14-16 ¹⁴C peaks of differing pI's containing the bulk of the bound carcinogen and no one component being labeled predominantly. The histone fraction was analyzed in a slab gel electrophoresis system. Only 23.5%-26% of the labeled carcinogen was recovered, and it was evenly spread out among the five histone components. These results indicate that although DNA appears to be the critical target in chemical carcinogenesis, the role of the various NHP species in the control of gene expression cannot be neglected. (16 refs)

79-0743 The Use of the D-T Diaphorase for the Detection of Foci of Early Neoplastic Transformation in Rat Liver. (Eng) Schor, N. A. (Dept. Pathology, Tulane Univ. Sch. Medicine, New Orleans, LA, 70112); Ogawa, K.; Lee, G.; Farber, E. *Cancer Lett* 5(3): 167-171; 1978.

Preneoplastic foci and hyperplastic nodules induced in rat liver by dietary acetylaminofluorene were analyzed for D-T diaphorase and glucose-6-phosphate dehydrogenase activity. The former enzyme was increased six times and the latter four times in the hyperplastic nodules. Histochemical staining techniques showed the localization of the diaphorase to be exclusively in the preneoplastic foci and in the liver nodules. These findings suggest that (1) neoplastic cells undergo at least two phenotypic changes, ie, the changes in the activity of these two enzymes in the early stages of carcinogenesis; (2) that D-T diaphorase may be useful for the quantitation of carcinogenicity in the liver; and (3) that D-T diaphorase may participate in the resistance of precancerous cells to the necrogenic action of chemical toxins. (20 refs)

79-0744 Biochemical Basis for the Resistance of Guinea Pigs to Carcinogenesis by 2-Acetylaminofluorene. (Eng) Kawajiri, K. (Biochemistry Div., Saitama Cancer Center Res. Inst., Ina-machi, Kitaadachi-gun, Saitama-362, Japan); Yonekawa, H.; Hara, E.; Tagashira, Y. *Biochem Biophys Res Commun* 85(3): 959-965; 1978.

The resistance of guinea pigs to 2-acetylaminofluorene (AAF)-induced carcinogenesis was investigated by examining the induction of cytochrome P-448 by 3-methylcholanthrene (MC) and the binding of AAF to the DNA in isolated guinea pig nuclei. Cytochrome P-448 and aryl hydrocarbon hydroxylase were not induced in either the microsomes or nuclei of guinea pigs by MC. MC caused only a 2-fold increase in the binding of AAF to DNA in guinea pig nuclei, but it caused a 17-fold increase in the binding to DNA in rat nuclei. The binding of N-hydroxy-2-acetylaminofluorene (N-OH-AAF), a proximate form of AAF, to DNA in nuclei of rats and guinea pigs was identical. It is concluded that there is a good correlation between the low inducibility of cytochrome P-448 and the low binding of AAF to DNA. The results indicate that guinea pigs are resistant to tumor induction of AAF through their inability to carry out the first step of AAF activation. (19 refs)

79-0745 Damage of Proliferating Lymphoid Cell Deoxyribonucleic Acid by Methyl Methanesulfonate and N-Acetoxy-2-acetylaminofluorene. (Eng) Warren, J. R. (Dept. Pathology, Northwestern Univ. Medical Sch., Chicago, IL, 60611). *Cancer Lett* 5(5): 253-260; 1978.

A method was developed for rapidly measuring carcinogen-induced damage to proliferating lymphocyte DNA by following changes in the rates of both DNA replicative and repair synthesis. DNA replicative synthesis by splenic lymphoid cells cultured from C57BL/6J mice and stimulated to proliferate with concanavalin A (Con A: 1.0 μ g/ml) was strongly suppressed during a short incubation (10-60 min) of the cells in medium containing methyl methanesulfonate (MMS: 0.2-0.8 mM) or N-acetoxy-2-acetylaminofluorene

(N-acetoxy-AAF: 0.005-0.01 mM). Carcinogen-treated lymphoid cells failed to recover stimulated levels of replicative synthesis after incubation for up to 3 hr in fresh medium without carcinogen. In contrast, spleen cells treated with hydroxyurea (HU), a metabolic inhibitor of DNA replication, fully recovered their ability for replicative synthesis when placed in fresh medium without added HU. In addition, the inhibition of replicative synthesis by the carcinogens was accompanied by marked stimulation of DNA repair synthesis. These results indicate that the rapid screening of carcinogenic and potentially carcinogenic chemicals for DNA-damaging properties should be possible by concomitant measurement of replicative and repair synthesis of DNA in *in vitro* cultures of proliferating lymphocytes treated with the test chemical. (20 refs)

79-0746 Inhibition of DNA-Repair and DNA-Synthesis by Harman in Human Alveolar Tumor Cells.

(Eng) Remsen, J. F. (Dept. Biochemistry and Molecular Biology, Univ. Florida, Box J245, JHMHC, Gainesville, FL, 32610); Cerutti, P. A. *Biochem Biophys Res Commun* 86(1): 124-129; 1979.

The effect of harman (HM), a tryptophan pyrolysis product, on colony-forming ability, DNA synthesis, and DNA repair was investigated in A549 human alveolar tumor cells. When A549 cells were treated for 48 hr with 25-200 μ M of HM, colony-forming ability decreased with increasing concentration. In addition, the size of the colonies was reduced at 200 μ M, indicating a significant increase in generation time. When A549 cells were prelabeled in their DNA with 14 C-thymidine, treated with HM for 10 min, and then pulsed for 15 min with 3 H-thymidine in the presence of HM, DNA synthesis capacity decreased to 29% of control values at 200 μ M HM. Since only 10 min preincubation with HM was required for inhibition of DNA synthesis, HM probably exerted its effect by direct interaction with chromatin. In additional experiments, A549 cells were prelabeled with 14 C-thymidine, treated with 25 μ M N-acetoxy-2-acetylaminofluorene (AAAF) for 15 min, and then incubated with and without 200 μ M HM. AAAF caused a rapid fragmentation of DNA that slowly reconstituted to the mol wt of untreated controls over 20-30 hr in the absence of HM. In the presence of HM, DNA fragmentation further increased during the first 4 hr, and slow elongation only occurred after 16 hr. Therefore, HM did not affect the immediate incision of damaged DNA, but it strongly inhibited a subsequent repair step. These results indicate that HM affects several processes that are thought to modify the mutagenic potency of procarcinogens and ultimate mutagens. (13 refs)

79-0747 Photosensitized Carcinogen Degradation and the Possible Role of Singlet Oxygen in Carcinogen Activation. (Eng) Greenstock, C. L. (Medical Biophysics Branch, Atomic Energy Canada Limited, Whiteshell Nuclear

Res. Establishment, Pinawa, Manitoba, Canada ROE 1LO); Wiebe, R. H. *Photochem Photobiol* 28(4/5): 863-867; 1978.

The dye sensitized photooxidation of various chemical carcinogens, including 2-acetylaminofluorene, benzo(a)pyrene, 9,10-dimethyl-1,2-benzanthracene and 4-nitroquinoline-N-oxide, was studied in the presence and absence of oxygen. Visible light from a filtered 150-watt Xe arc was used for photolysis, and carcinogen destruction was monitored spectrophotometrically. The carcinogens were solubilized in aqueous soln within micelles of various lipidlike surfactants. Photosensitized destruction of the carcinogens by several triplet sensitizers was observed. Enhanced damage in the presence of oxygen was also found. These results are consistent with the hypothesis that photochemical oxidative damage to carcinogens is produced in aerated soln via the sensitizer triplet state, possibly involving singlet oxygen. These manifold reactions are catalyzed by micelles that concentrate polycyclic hydrocarbons in the nonpolar environment within the micelles, where the exclusion of water probably increases reactive species lifetimes. This model photochemical system mimics the aerobic metabolic activation of chemical carcinogens, which is believed to be mediated partly by various forms of activated oxygen. (22 refs)

79-0748 Gas-Solid Chromatographic-Mass Spectrometric Confirmation of Low Levels of Acrylonitrile after Distillation from Food-simulating Solvents. (Eng) McNeal, T. (Div. Chemistry and Physics, Food and Drug Admin., Washington, DC, 20204); Brumley, W. C.; Breder, C.; Sphon, J. A. *J Assoc Off Anal Chem* 62(1): 41-46; 1979.

A gas-solid chromatographic-mass spectrometric method for confirming the presence of acrylonitrile (AN) monomer in food-simulating solvents is described. AN in aqueous food-simulating solvents is concentrated by adding methanol and distilling the AN-methanol azeotrope. AN in heptane is partitioned into water and azeotropically distilled with methanol. Levels as low as 0.01 ppm AN in the original food-simulating solvents can be confirmed. (5 refs)

79-0749 Malignant Transformation of Cryopreserved Early Passage Syrian Golden Hamster Cells by 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide. (Eng) Pienta, R. J. (Chemical Carcinogenesis Program, NCI, Frederick Cancer Res. Center, Frederick, MD, 21501); Lebherz, W. B.; Takayama, S. *Cancer Lett* 5(5): 245-251; 1978.

The malignant transformation of secondary cultures of Syrian golden hamster embryo cells prepared from cryopreserved primary cells by 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2) was studied. Each dish contained about 500 target cells seeded into 6×10^4 x-irradiated feeder cells. On the next day, AF-2 (0.05, 0.25, 0.5, 1.0, 2.0, or 5.0 μ g/ml) was added to the cultures, which were incubated for 8 days without re-

feeding. Typical morphological transformation was observed in three separate experiments. No transformation was seen in cultures treated with dimethyl sulfoxide or medium alone. The transformed cells grew in semisolid agar. Inoculation of nine nonimmunosuppressed suckling hamsters with 10^6 of these cells produced tumors as early as 9 days in some animals; all were positive at 63 days after inoculation. The tumors were spindle cell sarcomas or fibrosarcomas. Although a dose-response relationship was not observed, the system has merit for the qualitative determination of carcinogenicity. (12 refs)

79-0750 Carcinogenicity of N-Nitrosoephedrine in Rats. (Eng) Eisenbrand, G. (German Cancer Res. Center, Inst. Toxicology and Chemotherapy, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany); Preussmann, R.; Schmahl, D. *Cancer Lett* 5(2): 103-106; 1978.

The carcinogenicity of N-nitrosoephedrine (NED) was investigated in 32 male Sprague-Dawley rats administered the compound po (120 mg/kg 2x/wk). The first animal with forestomach (FS) papillomas died on day 374 after the beginning of the experiment. At this time, 22 animals were still alive. Of the remaining 21 animals, 13 died with tumors in the liver, lung, and FS and 2 with tumors at other sites. The overall tumor yield thus was 50%. The median time of death for the tumor-bearers was 522 days after the beginning of the experiment. All animals that died with hepatocellular carcinomas also showed lung metastases. In addition to the three animals that died with FS papillomas, one died with hyperkeratosis of the FS (day 583); another one with a hepatocellular carcinoma also had hyperplasia of the glandular stomach (day 588). The observation of hyperkeratosis, papillomas, and one squamous cell carcinoma of the FS suggests that the compound not only exhibits systemic effects, it is probably also a weak local carcinogen. There were no esophageal carcinomas, although NED is a close analog of a potent esophageal carcinogen. (4 refs)

79-0751 The Need for a Mammalian Test System for Mutagens: Action of Some Reducing Agents. (Eng) Stich, H. F. (Unit Environmental Carcinogenesis, B.C. Cancer Res. Centre, Vancouver, Canada); Wei, L.; Lam, P. *Cancer Lett* 5(4): 199-204; 1978.

The mutagenic activity of four reducing agents (cysteine, cysteamine, glutathione, and ascorbic acid) and hydrogen peroxide was tested in the *Salmonella typhimurium*/microsome mutagenicity test, in the DNA repair assay using human fibroblasts, and in the chromosome aberration test using Chinese hamster ovary cells. At nontoxic concentrations and in the presence and absence of Cu^{2+} , the test compounds did not significantly increase the frequency of mutations in the *Salmonella* test using strains TA98 and TA100. In the presence of Cu^{2+} , all of the test compounds induced

a marked DNA repair synthesis and a relatively high frequency of chromosome aberrations in cultured mammalian cells following a 3-hr exposure. The addition of catalase to the mixtures virtually eliminated the induction of DNA repair synthesis and greatly reduced the chromosome damaging effect of all four reducing agents. These results indicate that the use of several test subjects, including mammalian cells, is required to eliminate false negatives in mutagenicity screening. (13 refs)

79-0752 Danger from Aromatic Nitro- and Amino-Compounds. (Ger) Weber, H. (Werksarzt, Hoechst AG, 6230 Frankfurt/M.-Hochst, W. Germany). *Zentralbl Arbeitsmed Arbeitsschutz Proph* 28(8): 234-235; 1978.

Malignant bladder tumors are among the dangers of exposure to aromatic nitro and amino compounds. During 1967-1976, 17 cases of hemorrhagic cystitis and 5 bladder tumors that were caused by exposure to aromatic amino compounds were observed. Alcohol consumption enhances the toxicity of these compounds. (no refs)

79-0753 Analysis of N-Nitrosamines in Various Fruits and Vegetables. (Rus) Melamed, D. B. (Inst. Nutrition, Moscow, USSR); Kostiukovskii, Ia. L. *Vopr Pitan* (6): 64-69; 1978.

A fluorometric assay was employed for the routine evaluation of N-nitrosamines (NA) in various fruits and vegetables. The extractability of NA from plant samples ranged from 67.2% to 88.6%. Max levels of NA (up to 1.5 $\mu\text{g/kg}$) were detected in beets and radishes. It was concluded that the produce tested had relatively low levels of NA. (14 refs)

79-0754 Structure-Activity Relationships of Selected Nitrosamines. (Ger) Wenzel, U. (Sektion Pharmazie, Martin-Luther-Universität Halle-Wittenberg, Weinbergweg 15, DDR-402 Halle/Saale, E. Germany); Metzner, J. *Pharmazie* 33(11): 716-717; 1978.

Correlations between carcinogenicity and the physicochemical parameters of the substituents in N-nitrosodimethylamine, N-nitrosopyrrolidine, N-nitrosodiethylamine, N-nitrosoproline, N-nitrosodiamylamine, and N-nitrosodicyclohexylamine were studied. Carcinogenicity seems to increase with increasing lipophilia and molecule size. (8 refs)

79-0755 Significance of Nitrosamines in Animal Diets (Letter to Editor). (Eng) Edwards, G. S. (Cancer

Res. Div., Thermo Electron Corp., Waltham, MA, 02154); Fox, J. *Science* 203(4375): 6; 1979.

In a reply to a previous criticism, it is stressed that the contamination of laboratory animal feeds with up to 50 ppb N-nitrosodimethylamine (NDMA) can have a synergistic action with other (test) carcinogens, a statement supported by the literature. In addition, the study showed that 10 ppb NDMA in the drinking water of A/J mice during the fetal, weaning, and postweaning period up to 22 wk of age tripled lung tumor incidence from 8% to 23%. (5 refs)

79-0756 Dimethylnitrosamine-induced Structural Damage to DNA Results from Repair of O⁶-Methylguanine Rather than Repair of 7-Methylguanine. (Eng) Huang, P. H. (Sch. Pathology, Univ. New South Wales, P.O. Box 1, Kensington, N.S.W. 2033, Australia); Stewart, B. W. *Cancer Lett* 5(3): 161-166; 1978.

The hypothesis that single-stranded regions of DNA associated with the repair of O⁶-methylguanine (O-MG) are more readily bound to benzoylated diethylaminoethyl (DEAE)-cellulose than single-stranded regions associated with repair of 7-methylguanine (7-MG) was investigated by analyzing DNA labeled with ¹⁴C-dimethylnitrosamine (DMN) following primary fractionation on this cellulose. Female Wistar rats were injected ip with 10 mg/kg ¹⁴C-DMN (a nonnecrotizing dose) and sacrificed 4 or 24 hr later. DNA isolated from pooled livers was sheared and fractionated by chromatography on benzoylated DEAE-cellulose. Preparations of native DNA (NaCl-eluted) and DNA containing single-stranded regions (caffeine-eluted) were hydrolyzed and amounts of methylated guanine determined. Four hours after DMN injection, there was no difference in the distribution of 7-MG and O-MG between the two DNA fractions. At 24 hr, the amounts of 7-MG were still not different, but there was 10 times less O-MG in the caffeine-eluted DNA. This virtual absence of O-MG from caffeine-eluted DNA at this time implies that binding to benzoylated DEAE-cellulose was due exclusively to repair of O-MG. The qualitative distinction in the repair processes at 24 hr, defined in terms of the binding of particular single-stranded regions to benzoylated DEAE-cellulose, could be due to difference in size of the respective single-stranded regions and/or longer persistence of O-MG-derived single-stranded regions compared with those for 7-MG. (29 refs)

79-0757 DNA Repair Synthesis in Primary Cultures of Kidneys from BALB/c and C3H Mice Treated with Dimethylnitrosamine. (Eng) Brambilla, G. (Dept. Pharmacology, Univ. Genoa, Genoa, Italy); Cavanna, M.; Carlo, P.; Finollo, R. *Cancer Lett* 5(3): 153-159; 1978.

An in vivo-in vitro autoradiographic method was devised to study DNA repair in the kidneys of male BALB/c and C3H

mice following a single ip injection of dimethylnitrosamine (DMN: 38, 75, 150, or 300 mg/kg). Two hours after injection, kidneys were removed, minced, and 10,000 glomeruli and tubule fragments were incubated in culture with 1 μ Ci/ml ³H-thymidine. The level of unscheduled DNA synthesis was subsequently evaluated autoradiographically. Whereas unscheduled DNA synthesis was dose-dependent in the kidney cultures of both DMN-treated strains, it was practically absent in the cultures of control mice. The amount of synthesis was positively correlated with the differential susceptibility of C3H and BALB/c mice to kidney tumor induction by DMN, and it was 3 and 2.6 times higher in cultures from the former at 38 and 75 mg/kg, respectively. (22 refs)

79-0758 Dimethylnitrosamine Demethylase Activity of Rat Liver Microsomes after Partial Hepatectomy. (Eng) Evarts, R. P. (Carcinogen Metabolism and Toxicology Branch, NCI, NIH, Bethesda, MD, 20014); Mostafa, M. H. *Biochem Pharmacol* 27(23): 2751-2753; 1978.

The reason for the increased hepatocarcinogenicity of dimethylnitrosamine (DMN) following partial hepatectomy (PH) was investigated by determining liver DMN demethylase levels in male Wistar rats at 6, 24, 48, and 72 hr after median and left lateral lobe PH. In addition, the LD₅₀ for DMN administered 1 day after PH (50-156 mg/kg ip) was compared with that of control animals. The number of dead animals was recorded 44 hr after the injection, and the LD₅₀ was calculated from probit regression lines. Enzyme activity began to decrease at 6 hr post-PH and reached its lowest point (47%) at 24 hr; however, at 48 hr it had returned to approx 90% of control values. The LD₅₀ at 44 hr after injection was 114 mg/kg for PH animals and 82 mg/kg for controls. The reduced enzyme activity after PH indicates that increased DMN carcinogenicity after this operation is not caused by a compensatory increase in demethylase activity associated with liver regeneration. Rather, the results favor the idea that a slowing of DMN metabolism, while protecting against the acute toxicity of the drug, is a predisposing factor for carcinogenicity. (28 refs)

79-0759 Effects of N-Nitrosodiethylamine on Murine Hepatic Mixed-Function-Oxidase Activities. (Eng) Tucker, A. N. (Dept. Pharmacology, Medical Coll. Virginia, Richmond, VA, 23298); Tang, T.; Friedman, M. A. *J Environ Pathol Toxicol* 2(2): 571-578; 1978.

The effects of N-nitrosodiethylamine (DEN, 25-400 mg/kg po 24 hr before sacrifice, or 50 ppm in the drinking water for 12 wk) on the mixed-function oxidase activities of mouse liver were studied in male BALB/c mice. A single po dose of DEN resulted in a significant reduction in cytochrome P-450, aminopyrene demethylase, aniline hydroxylase, and DMN demethylase. The max effect was seen with 100 mg/kg DMN. Similar effects were observed in animals given DEN

in the drinking water for 12 wk. When S-9 fractions from the livers of mice treated with DEN were used to activate aflatoxin B₁, benzo(a)pyrene, and 2-acetylaminofluorene to mutagens in the Ames Salmonella mutagenesis test, activation was equivalent to or greater than that obtained using control S-9 fractions. The effects of DEN on aminopyrene demethylase could not be reproduced by collecting microsomes from homogenates that had been treated in vitro with DEN. The data support the concept that alteration of microsomal enzyme activities is an important effect of DEN. (13 refs)

79-0760 Genetic Activity of Chemicals in Yeast: DNA Alterations and Mutations Induced by Alkylating Anti-cancer Agents. (Eng) Ruhland, A. (Arbeitsgruppe Mikrobengenetik, Johann Wolfgang Goethe-Universitat, Robert-Mayer-Strasse 7-9, 6000 Frankfurt am Main, W. Germany); Fleer, R.; Brendel, M. *Mutat Res* 58(2/3): 241-250; 1978.

The alkylating anticancer agents nitrogen mustard, chlorambucil, triaziquone, activated cyclophosphamide, and half-mustard (2-dimethylaminoethylchloride) were tested for ability to produce primary DNA lesions and mutagenicity in *Saccharomyces cerevisiae* strains MB1072-2B, MB1113-8C, MB1114-5D, MB1114-16D, and MB1034-5A. Cross-links were detected by ultracentrifugation of the DNA in a neutral cesium chloride equilibrium density gradient. The formation of cross-links was correlated with time of application and with concentration of the alkylating agent. Nitrogen mustard was highly mutagenic in fully repair-proficient cells, less mutagenic in excision-deficient cells, even less so in postreplication repair-deficient cells, and was virtually nonmutagenic in cells lacking the excision-repair function. All the other mono-, bi-, and trifunctional alkylating agents tested were both mutagenic and lethal to differing extents. It appears that measurement of DNA interstrand cross-links is one of the more sensitive methods for detecting the genetic activity of polyfunctional alkylating agents. (36 refs)

79-0761 Induction of Thyroid Follicular Adenomas and Carcinomas by N-Nitrosobis(2-oxopropyl)amine. (Eng) Pour, P. (Eppley Inst. Res. Cancer; Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB 68105); Salmasizadeh, S. *Cancer Lett* 5(1): 13-18; 1978.

Thyroid follicular adenomas and carcinomas developed in MRC rats treated with N-nitrosobis(2-oxopropyl)amine (BOP) in a single dose (100 mg/kg sc) or in weekly doses (2.5, 5, or 10 mg/kg sc) for life. The single dose produced a tumor incidence of 0/1 in females and 2/4 in males; the respective weekly doses produced incidences of 9/15, 2/15, and 2/15 in females and 6/15, 5/15, and 6/15 in males. Tumor incidence was slightly higher and the latency period shorter in males, but the tumors were larger in females. No dose-re-

sponse relationship was seen. The actual tumor incidence may have been higher, as the small size of most of the neoplasms (1-2 mm) made them difficult to detect. In all, 32 rats developed 48 thyroid neoplasms, most of which were located in the midportion of the organ. Tumors were solid in 20 rats and multiple in 12. Morphologically, 38 tumors were adenomas (including follicular, papillary, follicular-papillary, and solid types) and 10 were carcinomas (follicular, follicular-papillary, and solid types). The possible mechanisms of BOP carcinogenesis are discussed. This experiment provides a model for investigating thyroid tumor etiology and an opportunity to elucidate the complexity of nitrosamine carcinogenicity. (13 refs)

79-0762 An Animal Model of Pancreatic Cancer Involving Whole Pancreas Transplantation. (Eng) Sayers, H. J. (Dept. Surgery, Univ. California Sch. Medicine, San Diego, CA); Dail, D. H.; Orloff, M. J. *Surg Forum* 29: 122-124; 1978.

Transplantation of the pancreas obtained from Syrian hamsters treated with 2,2'-dihydroxydi-n-propylnitrosamine (12.5 mg/wk, sc) for 18 wk into healthy recipients as a heterotopic, vascularized, pancreaticoduodenal isograft or more provides a unique model of metastasizing pancreatic cancer that resembles the human disease. (2 refs)

79-0763 Mutagenicity of Aliphatic Nitrosamines in *Salmonella typhimurium*. (Eng) Rao, T. K. (Biology Div., Oak Ridge Natl. Lab., P.O. Box Y, Oak Ridge, TN, 37830); Young, J. A.; Lijinsky, W.; Epler, J. L. *Mutat Res* 66(1): 1-7; 1979.

The mutagenicity of 25 aliphatic nitrosamines was assayed using *Salmonella typhimurium* strains TA1535, TA100, TA1537, and TA98 with and without metabolic activation (MA) by rat liver homogenates. All mutagenicity analyses included both a plate assay and a liquid suspension test. With the exception of the halogenated compounds, all of the nitrosamines required MA, with a preference for the phenobarbital-induced rat liver homogenate. Only two test compounds, nitrosobis(2-chloroethyl)amine and nitrosobis(2-chloropropyl)amine, were mutagenic without MA. Of the remaining compounds, nine were mutagenic after MA: diethylnitrosamine, di-n-propylnitrosamine, nitrosodi-n-butylamine, nitrosodiisobutylamine, nitrodiallylamine, nitrosobis(2-ethoxyethyl)amine, nitrosomethyl-2-phenylethylamine, nitrosoethylethanolamine, and nitrosodi-n-octylamine. The last two compounds had borderline activity. However, two compounds not carcinogenic in rats were mutagenic and nine carcinogens were not mutagenic, including six that are liver carcinogens in rats. Thus, the suggested close relationship between carcinogenicity and mutagenicity, as determined in the liver mi-

chrome-activated *Salmonella* test, is not supported by these results. (19 refs)

79-0764 **Carcinogenicity of Methylated Derivatives of N-Nitrosodiethylamine and Related Compounds in Sprague-Dawley Rats.** (Eng) Lijinsky, W. (Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD, 21501); Taylor, H. W. *J Natl Cancer Inst* 62(2): 407-410; 1979.

The carcinogenicity of four nitrosamines derived by substitution of methyl groups for hydrogen in N-nitrosodiethylamine (NDEA) was tested by administration to Sprague-Dawley rats in drinking water at approx equimolar concentrations (0.7-0.9 mM). Treatments were given on 5 days/wk for 30 or 50 wk, and animals were allowed to diet naturally or were killed when moribund. Although N-nitrosohexamethylenimine (NHMI: a cyclic nitrosamine tested for comparison) and N-nitrosodi-n-propylamine (NDPA) both produced a spectrum of tumors similar to NDEA, the former was the stronger carcinogen, being equally potent as NDEA and killing all treated animals by 40 wk. All these animals had tumors of the liver, esophagus, or nasal turbinates, and many had tumors in multiple sites, but NDPA-treated rats had a greater number of carcinomas of the esophagus than NHMI-treated rats, and NDPA induced only hepatocellular carcinomas in the liver, whereas NHMI produced mostly hemangioendothelial sarcomas. N-Nitrosodiisopropylamine was a comparatively weaker carcinogen, inducing only a significant number of tumors of the nasal turbinates. At the doses given, neither N-nitrosodiisobutylamine or N-nitrosodi-sec-butylamine was significantly carcinogenic. These results support the hypothesis that oxidation at the alpha carbon atom of nitrosamines is a significant step in carcinogenicity. (17 refs)

79-0765 **Liver Ornithine Decarboxylase During Phenobarbital Promotion of Nitrosamine Carcinogenesis.** (Eng) Farwell, D. C. (Inst. Medical Res., Camden, NJ, 08103); Nolan, C. E.; Herbst, E. J. *Cancer Lett* 5(3): 139-144; 1978.

The hypothesis that elevation of ornithine decarboxylase (ODC) is a specific and possibly essential biochemical event in the promotion of skin tumors was tested in Sprague-Dawley rats. The rats were fed a 25% casein diet and drinking water containing 40 ppm N-diethylnitrosamine (DEN) ad libitum for 4 wk, at which time DEN was discontinued and phenobarbital (PB: 500 ppm in the diet) was begun for up to 20 wk (Group 4). Other groups received the casein diet only (Group 1), casein diet + PB (Group 2), or DEN + casein diet (Group 3). PB was very effective in promoting liver tumors induced by DEN, as Group 4 animals had a tumor incidence of approx 80% vs 33% in Group 3. There was no observable alteration in ODC activity in the tumor tissue of

either of these groups compared with enzyme activity in normal liver tissue. The hepatic concentrations of spermine and spermidine were similarly unchanged. Therefore, the promotion of hepatocarcinogenesis by PB does not appear to encompass phenotypic changes that induce or maintain elevated ODC activity in the liver. (10 refs)

79-0766 **Carcinogenesis of Nitrosomethylundecylamine in Fischer Rats.** (Eng) Lijinsky, W. (Frederick Cancer Res. Center, P.O. Box "B", Frederick, MD, 21501); Taylor, H. W.; Mangino, M.; Singer, G. M. *Cancer Lett* 5(4): 209-213; 1978.

Nitrosomethylundecylamine (NMUA) was synthesized and administered to Fischer 344 rats by gavage in olive oil soln (23 mg/animal 2x/wk for 30 wk). Nineteen rats died with tumors in the liver and/or lung. In contrast to the activity of its homolog, nitrosomethyldodecylamine (NMDA), no bladder tumors were induced. The liver tumors were hepatocellular carcinomas and cholangiocarcinomas, and they were first seen in animals dying at 40 and 45 wk, respectively. The lung tumors were squamous cell carcinomas (the first at 43 wk) and alveolar cell adenomas and adenocarcinomas (the first at 42 wk). There were also two animals with esophageal squamous cell carcinomas and two with papillomas of the nonglandular stomach. The large difference in target sites for tumor induction between NMUA and NMDA is consistent with the hypothesis that the long even-numbered carbon chain of the latter is degraded by beta oxidation to a 4-carbon chain, which is the proximate carcinogen. Similar degradation of the undecyl chain would result in a 3-carbon chain. (8 refs)

79-0767 **Comparison of Bladder Carcinogenesis by Nitrosomethyldodecylamine in Sprague-Dawley and Fischer Rats Carrying Transplanted Bladder Tissue.** (Eng) Lijinsky, W. (Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD, 21501); Taylor, H. W. *Cancer Lett* 5(4): 215-218; 1978.

A comparison was made of nitrosomethyldodecylamine (NMDA) carcinogenesis in male and female Sprague-Dawley and Fischer 344 rats, each of which bore a portion of urinary bladder transplanted beneath the skin of the back. NMDA was given to each animal by gavage (25 mg in olive oil 2x/wk for 30 wk; total dose: 1,500 mg/rat). In animals in which the transplants survived until death, there was only one tumor, an anaplastic carcinoma in one of the Sprague-Dawley rats. A solid growth of epithelial cells that was interpreted as possibly being of preneoplastic significance was found in a second Sprague-Dawley rat. No tumors were present in the transplants in Fischer rats. There was a 100% incidence of transitional cell carcinomas in all host urinary bladders. A large percentage of the bladder tumors metastasized to the lungs. The Fischer rats appeared to be more sensitive than the Spra-

gue-Dawley rats to NMDA, since they died earlier of transitional cell carcinomas of the bladder. The bladder tumor appears to be the only neoplastic response of these two rat strains to NMDA, with no detectable lesions in the liver or other organs. (7 refs)

79-0768 Epithelial Alterations in Fetal Tracheal Explants of Syrian Golden Hamsters Exposed to Diethylnitrosamine In Utero. (Eng) Emura, M. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, 3000 Hannover 61, W. Germany); Richter-Reichhelm, H. B.; Mohr, U. *Cancer Lett* 5(2): 115-121; 1978.

The neoplastic effect of diethylnitrosamine (DEN) on fetal tracheal epithelia after transplacental exposure was determined by a combined in vivo-in vitro approach. Pregnant Syrian golden hamsters were injected ip with 200-400 mg/kg DEN on day 13, 14, or 15 of gestation. Fetuses were removed 3.5-4 hr after exposure. Fetal tracheas were dissected, divided into cranial and caudal portions, and incubated in organ culture for 4-6 wk. After intrauterine DEN exposure, the fetal tracheal explants were macroscopically similar to those of control animals for up to 25 days of cultivation. Between 25 and 42 days, however, 48/74 experimental specimens developed lesions of the epithelial lining, and they consisted of hyperplasia, focal squamous cell metaplasia, and dysplasia. These lesions were found more frequently in cranial explants (29/37) than in caudal explants (19/37), and the differences were most distinguishable in explants exposed to DEN on gestation day 15. No alterations occurred in the control explants. These findings support the view that cellular differentiation partially determines the susceptibility of the hamster's respiratory epithelium to the effects of chemical carcinogens such as DEN. (14 refs)

79-0769 Transplantable Ductal Adenocarcinoma of the Syrian Hamster Pancreas. (Eng) Scarpelli, D. G. (Dept. Pathology, Northwestern Univ., 303 E. Chicago Ave., Chicago, IL, 60611); Rao, M. S. *Cancer Res* 39(2, Part 1): 452-458; 1979.

Growth, morphology, and biochemical characteristics of a well-differentiated ductal adenocarcinoma induced in a female Syrian golden hamster by N-nitrosobis(2-oxopropyl)amine and transplanted surgically into the dorsum of weanling nude athymic male BALB/c mice and into the inguinal region of weanling inbred Syrian hamsters are described. The tumor grew rapidly in nude mice (12-fold size increase by 45 days) with metastases being common, while growth in the hamster was slow (3-fold increase by 45 days) with no metastases seen. Although the tumor largely retained morphological characteristics of a well differentiated adenocarcinoma after 4 or 5 passages in vivo in both species, an intense infiltration of the tumor by polymorphonuclear leukocytes without

necrosis or infection being present was noted in the hamster. The tumors produced mucin and rapidly and specifically bound ^{125}I -labeled secretin, although the degree of nonspecific binding was higher than that of control hamster pancreas (40.5% vs 23%, respectively). Unstimulated adenyl cyclase activity of the neoplasm was significantly greater than that of unstimulated normal hamster pancreas. Although secretin administration increased the level of 3'/5'cyclic AMP three-fold in pancreas of normal hamsters, it did not significantly change this level in neoplastic tissue. These results suggest the secretin receptors on the cell membranes of the neoplasm may be altered in comparison with normal pancreas. (47 refs)

79-0770 Formation of N-Nitroso Compounds from Drugs and Nitrite in Human Gastric Juice In Vitro. (Ger) Scheunig, G. (Zentralinstitut für Krebsforschung, Akademie der Wissenschaften, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany); Ziebarth, D. *Pharmazie* 33(11): 722-726; 1978.

The in vitro formation of N-nitroso compounds from 36 drugs containing tertiary amines as the active agent and from sodium nitrite was studied in the gastric juice of pentagastrin-stimulated humans. Nitrosamines (NA's) formed with four drugs: aminophenazone (APZ: concentration 120 mg/100 ml; NA yield 69%), Copyrkal (a commercial preparation of APZ: concentration 30 mg/100 ml, NA yield 43%), Analgin (methampyrone: concentration 100 mg/100 ml; NA yield 11%), and Bromhexin (bromohexine hydrochloride: concentration 5 mg/100 ml, NA yield 3%). The NA formation rate was highest at pH 2.0. APZ and Copyrkal formed nitrosodimethylamine and an unidentified NA, but Analgin and Bromhexin yielded only one unidentified NA each. The reaction between APZ, Copyrkal, or Bromhexin and the nitrite was completed in 25 min, that between Analgin and the nitrite in 1 min. The nitrite consumption of eight compounds that are able to compete with amines in the nitrosation reaction (amidosulfonic acid, ascorbic acid, urea, glutamine, glycine, ethylurethane, ethanolamine, and ammonium chloride) was investigated at different pH's. Only ascorbic acid and amidosulfonic acid showed considerable nitrite consumption. Although the nitrite consumption of ascorbic acid was practically independent of pH in the range of 2-5, that of amidosulfonic acid declined with rising pH. (51 refs)

79-0771 Development of Biliary and Hepatic Neoplasms in Guinea Pigs Treated with N-Nitrosobis(2-oxopropyl)amine. (Eng) Rao, M. S. (Dept. Pathology, Northwestern Univ. Medical Sch., 303 E. Chicago Ave., Chicago, IL, 60611); Pour, P. *Cancer Lett* 5(3): 31-34; 1978.

The carcinogenicity of N-nitrosobis(2-oxopropyl)amine (BOP), a potent pancreatic carcinogen in Syrian golden ham-

sters, was studied in male inbred strain 13 guinea pigs. A group of 29 animals was given two weekly doses of 70 mg/kg sc during weeks 1 and 2 followed by two weekly doses of 20 mg/kg during weeks 4 and 5, for a total cumulative dose of 65-78 mg BOP. Animals were observed until death or termination of the experiment at 55 wk. Of the 14 guinea pigs surviving beyond 30 wk, 7 developed cholangiocarcinomas and 2 hepatocellular carcinomas. Eight of these animals also had hyperplastic foci or nodules. Metastases to peritoneal fat were seen in two animals with cholangiocarcinomas and to the lungs in one with hepatocellular carcinoma. The livers of the 15 animals that died before 30 wk were pale, and many had multiple cystic lesions that increased in number over time. There was marked bile and oval cell proliferation in these animals plus fatty metamorphosis, hepatic cell necrosis, and hepatocyte intranuclear inclusions. Cholangiofibrosis was common (41%) in animals dying after 15 wk. Cholangiomas first appeared at 6 wk and reached an eventual incidence of 69%. No tumors were found in other organs and no changes were noted in the pancreas, which indicates that BOP is not a pancreatic carcinogen in the guinea pig. (19 refs)

79-0772 Chemical and Biological Implications of Organic Compounds Formed in Simulated and Real Urban Atmospheres. (Eng) Pitts, J. N. (Dept. Chemistry, Univ. California Statewide Air Pollution Res. Center, Riverside, CA, 92521). *Ecotoxicol Environ Safety* 2(2): 199-217; 1978.

To evaluate the health effects, atmospheric sources, transformations, and sinks of a variety of nitrogenous compounds and polycyclic aromatic hydrocarbons (PAH) in accordance with the US Clean Air Act, research was conducted on real and simulated urban atmospheres. A 50-meter³ outdoor chamber was used to monitor the reactions in air of approx 500 ppb of diethylamine or triethylamine (DEA or TEA) with 10-20 ppb of NO and NO₂ and trace amounts of HONO. Results of gas chromatography-mass spectrometry product analysis revealed that diethylnitrosamine (DEN) was readily formed from DEA in the dark (approx 3% yield) and destroyed by sunlight, whereas traces of DEN formed from TEA in the dark showed an increased yield (approx 2%) in sunlight. Other photo-oxidation products from both amines included known carcinogens such as dimethylnitrosamine and acetamide. In a separate experiment, species such as N₂O₃, HNO₃, HONO, CH₃ONO₂, HO₂NO₂, HCOOH, and H₂CO were identified by high-resolution Fourier transform-infrared spectroscopy (FT-IR) when a mixture of air, propylene, and NO, was irradiated by a solar simulator. With a second FT-IR spectrometer, ppb levels of HNO₃, NH₃, HCOOH, and H₂CO were identified in "aged" ambient photochemical smog. When organic extracts of ambient particulates were subjected to the Ames' *Salmonella typhimurium* assay, all of them showed frameshift-type mutagenic activity without metabolic activation. The results show that these urban samples must contain mutagens other than those that require treatment with S-9 liver homogenate for activity in the Ames'

test, and therefore it is suggested that these active mutagens are formed in atmospheric reactions of ambient PAH with compounds present in photochemical smog. (42 refs)

79-0773 Two Crops of Primary Lung Tumors in BALB/c Mice after a Single Transplacental Exposure to Urethane. (Eng) Anderson, L. M. (Walker Lab., Memorial Sloan-Kettering Cancer Center, Rye, NY, 10580). *Cancer Lett* 5(1): 55-59; 1978.

The induction of lung tumors by transplacental exposure to urethane was studied in BALB/c mice. Pregnant mice were injected with urethane (1 mg/g ip) on gestation day 17. The offspring were sacrificed at age 10-54 wk, and a complete necropsy was performed. Only lung adenomas were found. Tumor incidence was 3/25 mice aged 12 wk, 1/17 aged 36 wk, 2/8 aged 38-42 wk, and 9/17 aged 1 yr. The latter incidence was significantly greater than that in mice age 10-36 wk. The results suggest that most lung tumors resulting from urethane treatment did not appear until age 8-12 mo. There were, therefore, two distinct crops of tumors. The fact that the second crop arose coincidentally with the first spontaneous tumors in controls (age 38-40 wk) and at the time when aging begins in the mouse suggests involvement of age-related changes in the host. Aging-associated changes in immune system function may have stimulated the growth of latent lung tumors. Immunostimulation of slow-growing, weakly antigenic tumors may also account for the appearance of the second crop. The system used may be useful for studying tumor latency. In addition, the results suggest that carcinogenesis assays based on lung tumors in certain mouse strains should be of sufficient duration. (15 refs)

79-0774 Mutagenic Action of N-Nitroso Derivatives of Carbamate Insecticides (Carbaryl and Propoxur) on Mammalian Cells. (Pol) Tyrkiel, E. (Zaklad Toksykologii Sanitarnej, Panstwowy Zaklad Higieny, ul. Chocimska 24, 00-791 Warsaw, Poland); Palut, D.; Cybulski, J. *Rocz Panstw Zakl Hig* 29(5): 527-532; 1978.

The mutagenicity of N-nitrosopropoxur (single dose of 100-300 mg/kg po) and of N-nitrosocarbaryl (50-150 mg/kg ip) was studied in Wistar rats and mice, respectively. These compounds failed to induce chromosome aberrations in the bone marrow cells of the animals. (12 refs)

79-0775 Carcinogenic Effect of N-Nitrosobis(2-hydroxypropyl)amine in Rabbits. (Eng) Kondo, H. (Dept. Oncological Pathology, Cancer Center, Nara Medical Univ., 840 Shijocho, Kashihara, Nara 634, Japan); Ikeda, T.; Yoshimura, Y.; Hoshimura, H.; Konishi, Y. *Cancer Lett* 5(6): 339-343; 1978.

The carcinogenic effect of N-Nitrosobis(2-hydroxypropyl)amine (BHP) was studied in 2.5- to 3-mo-old male rabbits. Six rabbits were given 1,000 ppm BHP in their drinking water for 25 wk (av intake, 40.6 mg BHP/day), and the survivors were sacrificed 60 wk after the start of treatment. Five BHP-treated rabbits survived > 50 wk, and 4/5 had liver and lung tumors. All six control rabbits survived for 60 wk, and none developed tumors. The liver tumors were hepatocellular adenomas, hemangiomas, and angiosarcomas. The lung tumors were adenomas and hemangiomas. Massive liver cell necrosis was seen in the treated rabbit that died at 31 wk. The BHP effect in rabbits differs from that reported in hamsters, but it is similar to that in mice, rats, and guinea pigs. These results support the view that the carcinogenic effect of nitroso compounds is influenced by chemical properties or by tissue-specific and species-specific factors as well as by route of administration. (11 refs)

79-0776 Pulse Polarographic Determinations of Nitrosamines. Part I. Determination of N-Nitrosodiethanolamines in Grinding Fluids. (Eng) Samuelsson, R. (Dept. Analytical Chemistry, Univ. Umea, S-901 87 Umea, Sweden). *Anal Chim Acta* 102(1): 133-140; 1978.

Assessment of differential pulse polarography for the direct determination of N-nitrosodiethanolamine (NDEA) in aqueous media revealed that the optimum supporting electrolyte and pH were H_2SO_4 at pH 1-2. The detection limit was approx 5×10^{-8} M NDEA. When the procedure was applied to commercial grinding fluids, high NDEA levels were found (75 μM) with an accuracy > 92% and a precision of $\pm 8\%$. (22 refs)

79-0777 Comutagenic Effects Exerted by N-Nitroso Compounds. (Eng) Guttenplan, J. B. (New York Univ. Dental Center, New York, NY, 10010). *Mutat Res* 66(1): 25-32; 1979.

The effect of pretreatment with dimethylnitrosamine (DMN), N-methyl-N-nitrosourea (NMU), or N-ethyl-N-nitrosourea (NEU) on the sensitivity of *Salmonella typhimurium* strains TA100 and TA1530 to mutagenesis with other N-nitroso compounds was tested. Mutagenesis induced by DMN and NMU alone was characterized by biphasic dose- and time-response curves. At low concentrations of NMU (0.10 and 0.35 mM) or short incubation times with DMN (5 and 10 min), no mutagenic response was observed, but higher doses of NMU (1.0, 2.5, and 5.0 mM) or longer incubation times with DMN (20, 30, or 40 min) led to substantially increased mutagenesis. Bacteria pretreated with subthreshold doses of DMN, NMU, or NEU were more sensitive to several mutagens than untreated bacteria. NMU sensitized bacteria toward DMN, diethylnitrosamine, or NEU; DMN sensitized bacteria toward NMU; and NEU enhanced subsequent mutagenesis by NMU. Mutagenesis induced by methyl-methane-

sulfonate and N-propyl-N'-nitro-N-nitrosoguanidine was not significantly enhanced by NMU or NEU pretreatment, suggesting that the former mutagens act by different mechanisms. The growth phase of the bacteria had little effect on the percentage enhancement of mutagenesis caused by pretreatment. These results suggest that an important role for N-nitroso compounds in the initiation of mutagenesis and carcinogenesis may be one of sensitization. (25 refs)

79-0778 Phase-Specific Cytotoxicity In Vivo of Hydroxyurea on Murine Fibrosarcoma Cells Synchronized by Centrifugal Elutriation. (Eng) Grdina, D. J. (Section Experimental Radiotherapy, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030); Sigdestad, C. P.; Peters, L. J. *Br J Cancer* 39(2): 152-158; 1979.

The S-phase-specific cytotoxicity of hydroxyurea (HU: 1 mg/ml, ip) was tested using synchronized murine fibrosarcoma (FSa) cells lodged in the lungs of female CeHf/Bu mice. FSa cells from primary asynchronous cultures were separated and synchronized on the basis of size by centrifugal elutriation. Flow microfluorometry (FMF) was used to determine the cell-cycle parameters and the relative synchrony of the separated populations. After elutriation, FSa cells from each fraction and heavily irradiated unseparated tumor cells were injected iv into whole-body irradiated mice, and HU was injected 20 min later. The unseparated control population number was reduced 35% and the S-phase cells were reduced 33% by HU. In general, there were no appreciable differences in lung colony number in any of the elutriated control groups. HU reduced lung colonies to some extent in all mice except those injected with fractions containing largely G_1 cells. The max reduction (80%) in lung colonies occurred in mice injected with the cell fraction containing the larger percentage (65%) of S-phase cells. The results demonstrate the usefulness of this procedure as a rapid method for characterizing the phase specificity of chemotherapeutic drugs in vivo. (10 refs)

79-0779 Stimulation of Ultraviolet-induced Carcinogenesis by 1,3-Bis(2-chloroethyl)-1-nitrosourea. (Eng) Epstein, J. H. (Dept. Dermatology, Univ. California Sch. Medicine, San Francisco, CA, 94143). *Cancer Res* 39(2, Part 1): 408-410; 1979.

To evaluate the effect of noncarcinogenic levels of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) on the induction of cutaneous squamous cell carcinoma by carcinogenic levels of UVB radiation, 145 3- to 4-mo-old female HR hairless mice were divided into 4 treatment groups; Group 1 (40 mice) received topical applications of BCNU (0.5 mg in 0.1 ml acetone, 1x/wk) and UVB energy (1.25×10^3 millijoules/cm² 3x/wk) to the posterior half of their backs for the duration of the study (up to 13 mo); Group 2 (36 mice)

received acetone applications and UVB exposures; Group 3 (29 mice) received BCNU treatment only; and Group 4 (40 mice) received acetone applications only. Mice were examined regularly, and mice with tumors > 4 , > 50 , and > 100 mm³ were tabulated. No tumors occurred in Groups 3 or 4, but 100% of the Group 1 survivors and 94% of the Group 2 survivors developed tumors. Tumors > 4 mm³ occurred by 2.25 mo in Group 1 and by 2.5 mo in Group 2; tumors > 50 mm³ occurred by 3 mo in both groups; tumors > 100 mm³ occurred at 3 mo in Group 1 and at 3.25 mo in Group 2. There were 1.3 and 1.4 tumors/mouse in Groups 1 and 2, respectively. Most of the tumors > 4 mm³ appeared earlier in Group 1 (before 8 mo) than in Group 2 (before 10 mo) and grew more rapidly in Group 1 than in Group 2, indicating that BCNU had a promoting or cocarcinogenic effect on UVB-induced carcinogenesis. It is concluded that BCNU + UV induces tumors of all three sizes more rapidly than does acetone plus UV. Therefore, patients being treated with topical BCNU should avoid extensive sun or artificial UV irradiation. (18 refs)

79-0780 Genetic Basis of Susceptibility for Neuroblastoma Following Treatment with N-Methyl-N-nitrosourea and X-rays in *Xiphophorus*. (Eng) Schwab, M. (Genetisches Institut der Justus-Liebig-Universität Gießen, Heinrich-Buff-Ring 58-62, D-6300 Giessen, W. Germany); Kollinger, G.; Haas, J.; Ahuja, M. R.; Abdo, S.; Anders, A.; Anders, F. *Cancer Res* 39(2, Part 1): 519-526; 1979.

The susceptibility of 65 genotypes of *xiphophorus* (nonhybrids and interpopulational and interspecific F₁ and backcross hybrids) to neuroblastoma (NB) development following exposure to N-methyl-N-nitrosourea (MNU: 1 mM in aquarium water for 1 hr, 4x at 2-wk intervals) or whole-body x-irradiation (1,000 R for 45 min, 3x at 6-wk intervals) was studied. NB's were induced in 64/3,500 fish by MNU and in 4/5,500 fish by x-rays; no NB's were noted in equal numbers of control fish. A group of backcross genotypes carrying the "lineatus" chromosome was particularly susceptible, as 60/64 MNU-induced and all 4 radiation-induced NB's developed in the 605 and 859 respectively treated fish in this group. These fish were derived from *X. variatus* x *X. helleri* hybrids with the latter as the recurrent parent. NB's could not be induced in *X. variatus* or in the F₁ generation of (*X. variatus* x *X. helleri*), although both carry the lineatus chromosome, in *X. helleri*, which lacks this chromosome, or in lineatus-lacking segregants. The results imply that NB is triggered by somatic mutation of regulating genes suppressing another gene (located on the lineatus chromosome) that favors neoplastic transformation. The number of regulating genes may account for the differential susceptibility of fish carrying this chromosome. Susceptibility would be due to a monogenic regulating system, which can be impaired easily by a single mutation; this system can be produced by eliminating regulating genes during selective backcrossing. (59 refs)

79-0781 N-Ethyl-N-nitrosourea-induced Teratogenesis of Brain in the Rat. A Cellular and Cytoarchitectural Analysis of the Neocortex. (Eng) Hallas, B. H. (Dept. Biological Sciences, Purdue Univ., West Lafayette, IN, 47907); Das, G. D. *J Neurol Sci* 39(1): 111-122; 1978.

N-Ethyl-N-nitrosourea (ENU: 60 mg/kg) was administered iv to pregnant Wistar rats on gestation days 14-21 to study the effects of the carcinogen on the developing brain. Overall brain size, size of the neocortex, and number of nerve cells per slab of neocortex were reduced by ENU treatment. The effects were graded, being more severe in pups treated early in embryogenesis than in those treated late in gestation. The following histologic abnormalities also occurred in a graded fashion: reduction in the number of nerve cells with a resulting thinning of all six layers of the neocortex; reduction in the size of the perikarya from different layers; increased density of nerve cells in the neocortex; patchy distribution of hyperchromatic cells in the neocortex; reduction in the number of dendrites per pyramidal cell; and reduction in the length, thickness, and branching of dendrites. The orientation of the pyramidal cells and other neocortical neurons remained normal. The data indicate that ENU administered during embryogenesis has profound and lasting teratological effects on the CNS. (14 refs)

79-0782 Hematological and Histopathological Characteristics of Leukemias Induced by 1-Alkyl-1-nitrosoureas in Donryu Rats. (Eng) Ogiu, T. (Div. Pathology, Biological Safety Res. Center, Natl. Inst. Hygienic Sciences, Kamiyoga 1-18-1, Setagaya-ku, Tokyo 158, Japan). *Gann* 69(6): 781-791; 1978.

The hematologic and histopathologic features of leukemias induced in Donryu rats by 1-methyl-1-nitrosourea (MNU, 100 or 400 ppm in the drinking water), 1-ethyl-1-nitrosourea (ENU, 100 to 400 ppm in the drinking water), 1-propyl-1-nitrosourea (PNU, 150 to 600 ppm in the drinking water, 200 to 800 mg/kg as a single po injection, or 400 mg/kg as a single sc injection), and 1-butyl-1-nitrosourea (BNU, 400 ppm in the drinking water for 5 or 15 wk) were studied. A total of 242 leukemias were induced in 604 rats. The 23 myeloblastic leukemias were characterized by marked anemia, splenomegaly, and hepatomegaly, and the surface of the spleen was nodular in most cases. Survival was longest among the 74 rats with myelocytic leukemia; in this form, the WBC count was high, anemia and hepatosplenomegaly were marked, and leukemic cells invaded the periportal area of the liver. Survival was shortest in the 90 rats with erythroblastic leukemia, which was characterized by hepatomegaly, invasion of the sinusoids by leukemic cells, and adrenal involvement. The 27 cases of lymphoblastic leukemia were characterized by increased WBC count, anemia, slight hepatosplenomegaly, invasion of the hepatic periportal area by leukemic cells, and involvement of the lymphatic tissues. There were also 18 leukemic and 10 unclassified leukemias.

1-Alkyl-1-nitrosourea-induced leukemias in the rat are useful models for various human leukemias. (20 refs)

79-0783 Experimental Production of 'Keratin Pools' in the Rat Forestomach (Meeting Abstract). (Eng) Reibel, J. (Dept. Oral Pathology, Royal Dental Coll., Copenhagen, Denmark); Praetorius, F. *J Dent Res* 58(Special A): 301; 1979. (1 ref)

79-0784 Symposium on the Principles of Radiation Research Applied to Environmental Agents. The Concept of Drug Dose for In Vitro Studies with Chemotherapeutic Agents. (Eng) Wheeler, K. T. (Cancer Center, Div. Radiation Oncology, Univ. Rochester, Rochester, NY, 14642); Levin, V. A.; Deen, D. F. *Radiat Res* 76(3): 441-458; 1978.

Concepts of drug dose are defined, and pharmacokinetic and cell survival data collected from experiments in which rat 9L brain tumor cells were treated in vitro with 1,3-bis(2-chloroethyl)-1-nitrosourea and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea are used to illustrate the problems and principles involved in adequately assessing the appropriate drug dose in tissue culture. There are two kinds of drug dose analogous to those used in radiation dosimetry: exposure dose is the amount of drug to which cells are exposed in any given time period; and absorbed drug dose is the amount of the biologically active moiety bound to the whole cell or to the specific target in question. Drug dose is dependent on both the stability of the drug and on its concentration in the medium. Practical solutions to the experimental problems raised are presented for many of the situations in which pharmacokinetic data are either unobtainable or unavailable. The concepts illustrated should provide a more uniform framework for performing interpretable in vitro drug experiments. (6 refs)

79-0785 Mutagenicity Tests of Diflubenzuron in the Micronucleus Test in Mice, the L5178Y Mouse Lymphoma Forward Mutation Assay, and the Ames *Salmonella* Reverse Mutation Test. (Eng) MacGregor, J. T. (U.S. Dept. Agriculture, Western Regional Res. Center, Berkeley, CA); Gould, D. H.; Mitchell, A. D.; Sterling, G. P. *Mutat Res* 66(1): 45-53; 1979.

Diflubenzuron, a new commercial pesticide, was tested for mutagenic activity using the micronucleus test in mice, the L5178Y mouse lymphoma forward mutation test at the thymidine kinase locus, and the *Salmonella typhimurium*/microsome reverse mutation assay. No mutagenic effects were seen at concentrations up to 1,860 µg/plate in the *Salmonella* assay, 300 µg/ml in the L5178Y forward mutation test, and 1,500 mg/kg in the micronucleus test. Although the mean incidence of micronucleated polychromatic RBC in the

1,500 mg/kg group was higher than in the control group, the difference was not statistically significant. (25 refs)

79-0786 Sister Chromatid Exchanges in Lymphocyte Cultures of Patients Receiving Chemotherapy for Malignant Disorders. (Eng) Lambert, B. (Dept. Clinical Genetics, Karolinska Hosp., 104 01 Stockholm 60, Sweden); Ringburg, U.; Harper, E.; Lindblad, A. *Cancer Treat Rep* 62(10): 1413-1419; 1978.

The frequency of sister chromatid exchanges (SCE) in the peripheral lymphocytes of 19 patients receiving chemotherapy for different types of neoplastic disease was studied by the fluorescence plus Giemsa technique. The SCE frequency was also determined in 42 healthy subjects. Significantly increased SCE frequencies were noted in six patients 2-7 wk after 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) treatment and in one patient 2 wk after melphalan treatment. In one patient treated with prednimustine and one with 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboximide, high SCE frequencies just below the upper limit of the control range were recorded 1-2 wk after therapy. Nine other patients receiving cytostatic courses of methotrexate, thioTEPA, bleomycin, adriamycin, cyclophosphamide, actinomycin D, 5-fluorouracil, vincristine, and prednimustine showed normal SCE frequencies when studied from 3 days to several weeks after treatment. Full tumor doses of radiotherapy were given to 12 patients, but this treatment did not cause a long-lasting increase in SCE. It is suggested that CCNU and melphalan give rise to DNA lesions that are not easily repaired by cellular enzymes. These long-lived lesions could be important in mutagenesis and in the development of secondary neoplasms. (18 refs)

79-0787 Carcinogenicity and Mutagenicity Testing of Three Isomeric N-Nitroso-N-methylaminopyridines in Rats. (Eng) Preussmann, R. (Inst. Toxicology and Chemotherapy, German Cancer Res. Center, D 6900 Heidelberg 1, W. Germany); Habs, M.; Pool, B. L. *J Natl Cancer Inst* 62(1): 153-156; 1979.

The carcinogenicity and mutagenicity of three isomers, 2-, 3-, and 4-N-nitroso-N-methylaminopyridine (2-, 3-, and 4-NMPY), were tested and compared. In the carcinogenicity tests, female BD rats were divided into four groups and given either no treatment or by gavage 2-NMPY [5 mg/kg 1x/wk; median total dose (MTD), 250 mg/kg], 3-NMPY (1 mg/kg 4x/wk; MTD, 328 mg/kg), or 4-NMPY (10 mg/kg 2x/wk; MTD, 1,720 mg/kg). They were observed over their life spans, sacrificed when moribund, and examined for tumor growth. The 2-NMPY-treated animals developed 18 esophageal tumors (12 benign papillomas, 6 carcinomas). In addition, two hemangioendotheliomas of the liver were found that also might be causally related to the treatment. The first tumor was observed on day 268 of treatment, vs day 573 in

controls. 3- and 4-NMPY demonstrated no carcinogenic activity. In the Ames' mutagenicity assay, none of the NMPY's was mutagenic to *Salmonella typhimurium* strains TA98 and TA1537, but high concentrations of 2-NMPY showed mutagenic activity toward strain TA100 when incubated with the S-9 liver microsome fraction isolated from Aroclor 1254-stimulated male Sprague-Dawley rats. These results do not support a postulated reaction mechanism predicting that 3-NMPY would have a reactivity different from the other compounds based on the known difference in chemical reactivity of the three isomeric diazopyridines, potential proximate and ultimate carcinogens. However, this finding does not definitely prove that the diazopyridines are not reactive intermediates. (19 refs)

79-0788 A Study of the Competitive Nitrosations of Pyrrolidine, Ascorbic Acid, Cysteine and *p*-Cresol in a Protein-based Model System. (Eng) Massey, R. C. (Ministry Agriculture, Fisheries and Food, Food Lab. (Colney), Colney Lane, Norwich NR4 7UA, England); Crews, C.; Davies, R.; McWeeny, D. J. *J Sci Food Agric* 29(9): 815-821; 1978.

The effects of competitive C- and S-nitrosations on the formation of nitrosopyrrolidine (NPYR) were determined in a protein-based model system, and the results were compared with those of similar reactions performed in aqueous soln. The protein-based matrix was prepared at a moisture level of 75%, and competitive nitrosations of pyrrolidine with 0.1 M ascorbic acid, cysteine, or *p*-cresol were carried out at 37 C and pH 5.25. The reactions were studied for 1 wk and analyzed daily for NPYR and sodium nitrite. The results of the reactions were similar in the protein-based heterogeneous matrix and in aqueous soln, although nitrite depletion was consistently faster in the former than in the latter. The major factor influencing NPYR formation was the amount of nitrite available for N-nitrosation. Ascorbic acid, cysteine, and *p*-cresol all reduced the formation of NPYR by competing with pyrrolidine for the available nitrite, with ascorbic acid being the most efficient scavenger of free nitrite in both systems. A second pathway of NPYR formation, possibly involving protein (thiol)-bound nitrite, was found for the heterogeneous matrix. The effect of this mechanism became apparent in the presence of an efficient free-nitrite scavenger. (24 refs)

79-0789 Absence of Povidone-Iodine-induced Mutagenicity in Mice and Hamsters. (Eng) Merkle, J. (Dept. Industrial Hygiene and Toxicology, BASF Aktiengesellschaft, D-6700 Ludwigshafen/Rh., W. Germany); Zeller, H. *J Pharm Sci* 68(1): 100-102; 1979.

Povidone-iodine (P-I: iodine as I_3^- ion complex bonded to povidone; available I, 11.2%) was tested for mutagenicity in NMRI mice by the dominant lethal assay (DLA) or the mi-

cronucleus test (MT) and in Chinese hamsters by the bone marrow test (BMT). In the DLA, 20 male mice received 72 mg/kg P-I ip and were mated to 3 females each. The conception rate decreased significantly only during the first week, and the av number of implantations and the mutagenicity index were not affected at any time. In the MT, 10 mice received two 36-mg/kg doses of P-I ip at an interval of 24 hr and were then sacrificed 6 hr later. Bone marrow smears were prepared, and 4,000 normochromatic and 2,000 polychromatic RBC were examined/animal. Although there was a slight increase in polychromatic RBC containing micronuclei, this increase was within the normal range. In the BMT, groups of 12 animals received single P-I doses of 38.3 or 82.5 mg/kg ip or five daily ip injections of 38.3 mg/kg on 5 successive days. There was no difference from controls in the percentage or type of aberrant metaphases seen when the substance was administered singly or repeatedly. None of these three tests revealed any evidence of a mutagenic effect for P-I. (6 refs)

79-0790 Spin Trapping of Free Radicals Produced from Nitrosoamine Carcinogens. (Eng) Floyd, R. A. (Biomembrane Res. Lab., Oklahoma Medical Res. Foundation, 825 Northeast Thirteenth St., Oklahoma City, OK, 73104); Soong, L. M.; Stuart, M. A.; Reigh, D. L. *Photochem Photobiol* 28(4/5): 857-862; 1978.

The spin trap 5,5-dimethylpyrroline-1-oxide (DMPO) was utilized to investigate nitrosoamine carcinogens by electron spin resonance spectroscopy. Incubation of 10-20 mM 1-nitrosopiperidine with rat liver microsomes or nuclei at 37 C in the presence of DMPO (20 mM) yielded a trapped hydroxyl free radical and a spin-trapped free radical of the carcinogen whose structure is unknown. Oxygen was required to produce the trapped hydroxyl radical, but formation of the nitrosoamine radical was enhanced in the absence of oxygen. Cyanide (0.5 mM) or α -tocopherol acetate (1 mM) reduced the amount of nitrosoamine trapped radical in the reaction, whereas preheating microsomes at 70 C for 10 min enhanced its formation. Dimethylnitrosamine, diethylnitrosamine, and 1-nitrosopyrroline yielded a similar pattern of trapping two radicals when studied in this reaction, although the structure of the trapped carcinogen radical obviously differed. The amount of radical produced was not proportional to the cytochrome P450 content. It is suggested that the unknown free radical of the trapped nitrosoamine could be the hydroxy alkyl free radical. (25 refs)

79-0791 Ritalin, Benzedrine and Dexedrine Do Not Transform F1706 Rat Cells. (Eng) Price, P. J. (Center Disease Control, Building 1, Room 3237, 1600 Clifton Rd, N.E., Atlanta, GA); Gregory, E. A.; Skeen, P. C. *Cancer Lett* 5(6): 345-349; 1978.

Ritalin (methylphenidate hydrochloride), Benzedrine (am-

phetamine sulfate), and Dexedrine (dextroamphetamine sulfate), frequently prescribed CNS stimulants, were examined for oncogenicity using a serial line of Fischer rat embryo cells. This line was previously shown to be a sensitive and accurate indicator of chemicals carcinogenic for rodents. In the transformation assay, rat embryo cells were incubated with 20 $\mu\text{g}/\text{ml}$ (max nontoxic dose) or 40 $\mu\text{g}/\text{ml}$ (LD_{50}) of one of the three drugs. Tumorigenicity was determined by injection of treated cells into newborn Fischer rats (5×10^5 cells sc). 3-Methylcholanthrene (3-MC: 0.2 $\mu\text{g}/\text{ml}$) was a positive control. All the 3-MC-treated cultures developed transformed foci within four subcultures after removal of the chemical. Cultures treated with one of the three drugs or acetone were phenotypically normal at the end of the experiment (after 8 subcultures) and produced no foci in agar. Only the 3-MC-treated cultures were tumorigenic in the newborn rats. These results are reported to add to the data base necessary for determining the relevancy of in vitro mammalian cell assays, and not to indicate that the drugs are safe for humans. (6 refs)

79-0792 Levels of Glutathione, Glutathione Reductase and Glutathione S-Transferase Activities in Rat Lung and Liver. (Eng) Moron, M. S. (Dept. Biochemistry, Arrhenius Lab., Univ. Stockholm, S-106 91 Stockholm, Sweden); DePierre, J. W.; Mannervik, B. *Biochim Biophys Acta* 582(1): 67-78; 1979.

Levels of glutathione (GSH), glutathione reductase, and glutathione S-transferase activities in the lung and liver of male Sprague-Dawley rats were investigated. After the lung was perfused to remove contaminating blood, an apparent concentration of 2 mM GSH was detected in this organ; the liver contained five times as much GSH. A single liver cell contained 11 times as much GSH as a lung cell. Rat lung tissue contained very little GSH disulfide (0.060 mM); rat liver tissue has been reported to contain very low levels of this substance (0%-8% of the GSH concentration). There were no significant differences in the levels of reduced GSH in lung or liver of rats pretreated with phenobarbital (80 mg/kg 1x/day ip for 5 days) or methylcholanthrene (20 mg/kg 1x/day ip on 5, 3, and 1 day before killing). The activities of GSH reductase and GSH S-transferase assayed with four different substrates were 5-60 times lower in lung than in liver. The relative levels of GSH and GSH S-transferase activities in the liver and lung may be an important factor in the relative susceptibility of these organs to the toxic and carcinogenic effects of xenobiotics and their metabolites. (38 refs)

79-0793 Induction of Mixed-Function Oxidases in Mouse Liver by Psoralens. (Eng) Mandula, B. B. (Dept. Dermatology, Massachusetts General Hosp., Boston, MA, 02114); Pathak, M. A.; Nakayama, Y.; Davidson, S. J. *Br J Dermatol* 99(6): 687-692; 1978.

The induction of mixed-function oxidases in mouse liver was determined following po or ip treatment of male CD-1 mice with 100 mg/kg 8-methoxypsoralen (8-MOP), 4,5',8-trimethylpsoralen (TMeP), psoralen, or phenobarbital. 8-MOP or phenobarbital induced a 2.5- to 3-fold increase in p-nitroanisole-O-demethylase (pND) activity in mouse liver homogenates. 8-MOP also increased the arylhydrocarbon hydroxylase (AHH) activity of the homogenates, whereas TMeP and psoralen did not increase either pND or AHH activity. Similar results were obtained with liver microsomes. The pND and AHH activities increased with increasing 8-MOP dose between 25 and 100 mg/kg. Enzyme induction was barely detected after treatment with 10 mg/kg 8-MOP. These results may have relevance in understanding the clinical differences in skin photosensitizing activity and the photochemotherapeutic effectiveness of the psoralens in diseases such as psoriasis and vitiligo. (24 refs)

79-0794 Demonstration of Mutagenicity with the Ames Salmonella/Microsome Assay. (Hun) Ferencz, A. (Komaron megyei Kozegeszsegugyi-Jarvanyugyi Alomas, Tatabanya, Hungary); Kiss, K.; Pinter, A.; Nadasdi, L.; Bornemisza, E.; Csinady, L. *Egeszsegudomány* 22(4): 379-387; 1978.

Experience with the Ames *Salmonella typhimurium*/microsome mutagenicity assay is reviewed. *Salmonella* strains TA1535, TA1537, TA1538, TA98, and TA100 were found to retain their genetic characteristics in the assay. Both the filter disk and the plate were suitable for detecting the mutagenicity of streptozotocin. The former is recommended for screening potentially mutagenic environmental chemicals and the latter is recommended for a more precise characterization of a mutagen. (16 refs)

79-0795 Ultrastructural Nuclear Changes in Human Lymphocytes Following Arabinosylcytosine Treatment In Vitro. (Eng) Conforti, A. (Istituto di Patologia Generale, Policlinico Umberto I, Viale Regina Elena no. 324, I-10000 Rome, Italy); Albani, L. M.; Modesti, A.; Leopardi, S.; Felici, L. *Virchows Arch Cell Pathol* 28(4): 301-308; 1978.

Treatment of synchronous normal human lymphocytes during the G_1 phase with 0.5 mg/ml cytosine arabinoside produced alterations in the nuclear envelope that closely resembled the malignancy-associated changes seen in human leukemic cells. The changes which occurred in an av of 5.4/1,000 cells consisted of blebs, pockets, filamentous invaginations, and projections containing nuclear or cytoplasmic material, and they were not seen in untreated cells. (27 refs)

79-0796 Complex Formation Between Pyrene and the Nucleotides GMP, CMP, TMP and AMP.

(Eng) Lianos, P. (Dept. Physics, Univ. Tennessee, Knoxville, TN, 37916); Georgiou, S. *Photochem Photobiol* 29(1): 13-21; 1979.

A study of the optical properties of the complexes formed between pyrene and nucleotides revealed that pyrene forms ground and excited electronic state complexes of 1:1 stoichiometry with guanosine, cytidine, and thymidine 5'-phosphate disodium salts and AMP. Ground and excited state association constants are presented. Partial transfer of charge from pyrene to nucleotide may play a role in complex formation. (24 refs)

79-0797 Synthesis and Properties of O⁶-Methyldeoxyguanylic Acid and Its Copolymers with Deoxycytidylic Acid. (Eng) Mehta, J. R. (Dept. Pharmacology and Experimental Therapeutics, Albany Medical Coll. Union Univ., Albany, NY, 12208); Ludlum, D. B. *Biochim Biophys Acta* 521(2): 770-778; 1978.

O⁶-Methyldeoxyguanosine triphosphate (m⁶dGTP) was synthesized from deoxyguanosine first protected by acetylation of the sugar hydroxyls and then chlorinated in the 6-position with POCl₃. The product was converted to O⁶-methyldeoxyguanosine and phosphorylated in the 5' position. Monophosphate was converted to the triphosphate and copolymerized with deoxycytosine triphosphate by terminal deoxynucleotidyl transferase. The resulting template, which contained O⁶-methylguanine, was tested for its ability to direct RNA synthesis by bacterial RNA polymerase. O⁶-Methylguanine led to the misincorporation of uridine monophosphate in the product polymer, supporting the hypothesis that O⁶-methylguanine is a promutagenic base. (20 refs)

79-0798 Effect of Misonidazole (Ro-07-0582) on the Incidence of Micronuclei in Irradiated Ehrlich Tumour Ascites Cells. (Eng) Olinici, C. D. (Inst. Oncology, Republicii 34-36, R-3400 Cluj-Napoca, Romania); Mustea, I. *Int J Radiat Biol* 34(6): 589-593; 1978.

The effect of misonidazole (MNZ), a potent hypoxic radiosensitizing chemical, on the incidence of micronuclei was studied in irradiated Ehrlich ascites cells in NMRI male mice. The animals received MNZ (0.5 mg/g ip) 30 min prior to irradiation with 100, 200, or 400 R. Animals in each group were killed 24, 48, and 72 hr after irradiation, and the frequency of micronuclei in ascites cells was calculated after 2,000 cells were scored in each animal. Irradiation induced a dose-dependent increase in the frequency of micronuclei. A further enhancement of micronuclei formation was observed in the groups pretreated with MNZ. The largest number of micronuclei was reached 72 hr after irradiation in control groups irradiated with 100 and 200 R and in the MNZ-treated group irradiated with 100 R, and 48 hr after irradiation in the control group irradiated with 400 R and

in the MNZ-treated group irradiated with 200 and 400 R. These results show that MNZ pretreatment increased the incidence of micronuclei in irradiated tumor cells, and they suggest the possibility of using the micronucleus assay for screening substances with a radiosensitizing potential. (15 refs)

79-0799 The Effect of Several Lymphocytotoxic Agents on Murine Leukemogenesis. (Eng) Menahan, L. A. (Dept. Pharmacology, Medical Coll. Wisconsin, Milwaukee, WI, 53233); Kemp, R. G. *Life Sci* 23(16): 1687-1692; 1978.

The actions of the lymphocytotoxic agents cortisone (CTS), 5'-azathioprine (AZT), and 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboximide (DTIC) on leukemogenesis in male AKR/J and male ARS HA/1CR (Swiss albino) mice were compared. CTS (1 mg) was injected sc for 3 consecutive days on two occasions 1 mo apart; AZT (17 3-mg doses) was injected into the thigh over a period of 8 wk (3 doses/wk for 1 mo; 2 doses for 1 wk; 1 dose/wk for 3 wk), and DTIC was injected once ip into both strains in doses ranging from 240 to 530 mg/kg. Both CTS and AZT prolonged survival in AKR/J mice, whereas DTIC induced lymphomas after a 70-day lag period in >90% of both AKR/J and Swiss albino mice. All DTIC-treated mice had grossly enlarged thymuses and most had enlarged spleens. In short term experiments, all three agents reduced the population of medium-sized lymphocytes in the thymus within 48 hr, and CTS and DTIC also led to a reduction in spleen wt. The results of the DTIC experiment indicate that it could be a model for studying critical events in the preleukemic state. (7 refs)

79-0800 Acute Myelomonocytic Leukemia Following a Chemotherapeutic Regimen for Metastatic Sarcoma. (Eng) Youness, E. (Dept. Lab. Medicine, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030); Dosik, G.; Benjamin, R. S.; Trujillo, J. M. *Cancer Treat Rep* 62(10): 1513-1516; 1978.

A 64-yr-old woman developed acute myelomonocytic leukemia (AML) in June 1977, 18 mo after treatment with a protocol of cyclophosphamide, vincristine, adriamycin, and 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (the CyVADIC regimen) for a metastatic sarcoma. The patient had had no prior history of radiation. In 1973, an adenocarcinoma (Grade I) with superficial myometrial invasion and a hemorrhagic leiomyoma were identified upon abdominal hysterectomy and bilateral salpingo-oophorectomy. In December, 1975, the patient was diagnosed as having metastatic sarcoma suggestive of leiomyosarcoma after a left thoracotomy was performed for multiple pulmonary nodules. Chemotherapy was initiated at this time. In March 1976, she was discharged in partial remission, but in November the

pulmonary nodules had increased in size. Substitution of actinomycin D for adriamycin in February 1977 was not helpful, and monocytosis was noted in a peripheral blood smear at this time. In June 1977, she was treated with cis-dichlorodiammineplatinum (II) to control metastatic disease. The clot section of a bone marrow aspiration revealed marrow particles with a cellularity of 70% and sheets of immature myelomonocytic cells. Results of bone marrow smear, special staining, and complete blood count led to the diagnosis of AML. This is the first known case of leukemia in > 400 trials of the CyVADIC regimen. (31 refs)

79-0801 Development of an Intestinal Cell Culture Method to Study Dietary Effects of Intestinal Mutagens. (Eng) Lee, W. Y. (Michigan State Univ., East Lansing, MI, 48832). *Diss Abstr Int B* 39(7): 3248B; 1979. (no refs)

79-0802 Repair of O⁶-Methylguanine in Adapted *Escherichia coli*. (Eng) Schendel, P. F. (Imperial Cancer Res. Fund, Mill Hill Labs., Burtonhole Lane, London, NW7 1AD, England). *Proc Natl Acad Sci USA* 75(12): 6017-6020; 1978.

The chromatographic spectra of alkylated purines found in adapted and control *Escherichia coli* cells exposed to N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) were analyzed. [The cells were adapted by previous exposure to sublethal concentrations of MNNG (0.05 and 0.5 µg/ml).] During exposure to 5 or 10 µg/ml MNNG, the adapted cells accumulated substantially less O⁶-methylguanine (OMG) in their DNA than control cells; accumulations of 7-methylguanine and 3-methyladenine were similar. The adapted cells reduced the accumulation of OMG in their DNA by reducing the O⁶ methylation of guanine and by rapidly removing the OMG when it did form. However, the repair component of the adaptive response was limited and it ceased to function if the amount of methylation became too great. When this happened, OMG started to accumulate, and the cells began to develop mutations at a rate directly proportional to their rate of OMG accumulation. The data support the idea that the O⁶ methylation of guanine accounts for most MNNG-induced mutagenesis. (20 refs)

79-0803 Modification of Rat Liver Chromatin by N-Methyl-N'-nitro-N-nitrosoguanidine or N-Ethyl-N'-nitro-N-nitrosoguanidine and Template Activity for RNA Synthesis by *Escherichia coli* RNA Polymerase after Reconstitution. (Eng) Yoda, K. (Div. Biochemistry, Chiba Cancer Center Res. Inst., 666-2, Nitona-Cho, Chiba 280, Japan); Sakiyama, S.; Fujimura, S. *Biochim Biophys Acta* 521(2): 677-688; 1978.

The binding of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) to the DNA, histones, and nonhistone chromosomal proteins (NHCP) of Donryu rat liver chromatin was studied. The binding of MNNG and ENNG to histones or NHCP increased linearly with time up to 6 hr. MNNG showed greater binding than ENNG, and the binding of the guanidino moiety of either compound was greater than that of the corresponding alkyl moiety. The binding of both compounds to DNA, however, was very low. In order to compare the effect of modification of each component of chromatin by MNNG or ENNG, each component modified separately was reconstituted with the two other intact components. Then, ³H-uridine monophosphate incorporation into acid-insoluble material was measured using *Escherichia coli* RNA polymerase. The template activity of whole chromatin for RNA synthesis was similar to that of untreated reconstituted chromatin. However, the template activity of reconstituted chromatin containing MNNG-modified histones was increased about 10-fold and the template activity of reconstituted chromatin containing ENNG-modified histones was increased about 5-fold. Modification of the NHCP or DNA of reconstituted chromatin had no effect on template activity. The template activity of whole chromatin treated with MNNG or ENNG increased approx two-fold over that of untreated whole chromatin. (33 refs)

79-0804 Inactivation of N-Methyl-N'-nitro-N-nitrosoguanidine in the Ames *Salmonella*/Microsome Test. (Eng) Gentile, J. M. (Dept. Biology, Hope Coll., Holland, MI, 49423); Overton, L. K.; Schubert, J. *Naturwissenschaften* 65(12): 659-660; 1978.

The mutagenic deactivation of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) by various fortified rat liver homogenate (S-9) preparations in the Ames *Salmonella* test was investigated. The mutagenicity of MNNG decreased proportionately with the milligrams of protein of S-9 added per plate. However, when NADPH was omitted from the reaction mixture or when the *Salmonella* were incubated with bovine serum albumin or various maize tissue homogenates, no decrease in MNNG mutagenic activity was observed. These data indicate that an NADPH-dependent enzyme(s) in standard S-9 preparations inactivates MNNG. This was confirmed by the observation that S-9 preparations in which the metabolizing enzymes had been inactivated by heat, pH variation, and treatment with 4-chloromercuribenzoic acid failed to inactivate MNNG. The promutagens aflatoxin B₁ and 2-anthramine required the addition of S-9 before their mutagenic activity was observed. Ethyl methane sulfonate and streptozotocin were unaffected by the addition of S-9, but N-ethyl-N'-nitro-N-nitrosoguanidine was deactivated by this preparation. Since the mutagenicity of a known and powerful carcinogen such as MNNG can be modified or eliminated by simplistic means in standard mutation assays, it may be premature to accept routinely the results of mutagenic-carcinogenic potency correlations. (16 refs)

79-0805 Formation of Methylnitrosocyanamide from Methylguanidine and Sodium Nitrite in Simulated Gastric Juice and in Stomachs of Rats: Quantitative Estimation by a Mutagenicity Assay. (Eng) Ishizawa, M. (Dept. Hygiene, Faculty Medicine, Kyushu Univ., Higashi-ku, Fukuoka 812, Japan); Utsunomiya, T.; Kinoshita, N.; Endo, H. *J Natl Cancer Inst* 62(1): 71-77; 1979.

The formation of methylnitrosocyanamide (MNC), a carcinogenic N-nitroso compound, from methylguanidine (MG) and NaNO_2 in simulated gastric juice (SGJ) and in the stomachs of male Wistar rats was quantitatively investigated. In the *Salmonella typhimurium* reverse mutation assay using strain TA1535, MNC formation increased linearly for about 40-60 min after the incubation of MG with NaNO_2 in SGJ. Thereafter, however, it decreased rapidly. The initial rate of MNC formation was directly proportional to the initial molar ratio of MG to NaNO_2 , but the yields of MNC depended only on the amount of MG added and were fairly constant (0.3%-0.5% of the initial MG). MNC did not form at a pH above 2.5 or in the presence of 2% casein in SGJ at pH 1.2. It decomposed rapidly in SGJ at pH 1.2 with a half-life of approx 2 min, whereas it was stable in phosphate buffer at pH 7.0. Following concurrent administration of MG and NaNO_2 via stomach tube, MNC formation was detected in the pylorus-ligated stomachs of rats preconditioned with a casein-free dextrin diet but not in those of rats preconditioned with a casein-containing or synthetic diet. The yields of MNC observed 40-60 min after administration of reactants ranged from 0.02% to 0.05% of the initial MG. The possible environmental significance of MNC formation in vivo is considered. (24 refs)

79-0806 Carcinogenic Effect of a Guanidine Pesticide Administered with Sodium Nitrite on Adult Mice and on the Offspring after Prenatal Exposure. (Eng) Borzsonyi, M. (Natl. Inst. Hygiene, H-1966 Budapest, Hungary); Pinter, A.; Surjan, A.; Torok, G. *Cancer Lett* 5(2): 107-113; 1978.

The carcinogenicity of the fungicide dodecylguanidine acetate (DGA, dodine) was studied in pregnant Swiss/Leiden mice and their offspring. On gestation days 15-21, the females were given 6 or 40 mg/kg DGA and 10 mg/kg sodium nitrite intragastrically plus 0.1% sodium nitrite in the drinking water. Controls received DGA or sodium nitrite alone or were untreated. Most of the resulting tumors were lymphosarcomas, and the incidence in the female parents given 6 and 40 mg/kg DGA was 47.1% and 52.9%, respectively. The first tumor appeared 4 mo after delivery. The incidence in the offspring was 22.9% and 50% in males and 32.6% and 43.8% in females at the two respective doses. Thus, the carcinogenicity of DGA was dose-dependent. The first tumors appeared at 6-7 mo. The spontaneous incidence of lymphosarcomas in untreated controls was approx 1% by 10 mo. DGA alone and sodium nitrite alone had no effect on cancer incidence. A few lung adenomas were seen in the experimen-

tal animals. The high incidence of lymphosarcomas in the adult females could be due to the increased levels of estrogens during pregnancy. A- and C-type RNA virus particles were found in the tumor cells by electron microscopy. (20 refs)

79-0807 Tumor Induction in the Glandular Stomach of Rats after Oral Administration of a Single or a Few Doses of N-Methyl-N'-nitro-N-nitrosoguanidine During the Newborn Period. (Eng) Sumi, Y. (Lab. Germfree Life Res., Nagoya Univ. Sch. Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466, Japan); Miyakawa, M. *Gann* 69(6): 805-812; 1978.

The carcinogenicity of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in newborn male and female Wistar rats was studied. MNNG was given po (using a catheter technique) as a single dose (100 μg) to animals less than 24-hr-old (Group 1) and as 3 consecutive daily doses (150 μg each) to rats aged 2 to 5 days (Group 2). Survival to 30 days after the first dose was high and the carcinogen had no effect on body wt. Adenocarcinomas of the fundic and pyloric stomach were found in 5/19 Group 1 rats and 15/33 Group 2 rats surviving until day 473 after the first dose. The tumors frequently invaded the serosa, and metastases to other portions of the digestive system were observed in two animals. Leiomyosarcomas were found in one Group 1 rat and three Group 2 rats, carcinosarcomas were found in one animal from each group, and a squamous cell carcinoma was found in one Group 2 rat. In addition to these tumors, all of which occurred in the glandular stomach, two adenomas of the liver and two adenocarcinomas of the duodenum were observed, as were several benign tumors. (16 refs)

79-0808 Synthesis of 4-(N-Hydroxy-N-methylamino)quinoline 1-Oxide and Its Carcinogenic Activity on Mice. (Eng) Kawazoe, Y. (Faculty Pharmaceutical Sciences, Nagoya City Univ., Tanabe-dori, Mizuho-ku, Nagoya 467, Japan); Ogawa, O.; Takahashi, K.; Sawanishi, H.; Ito, N. *Gann* 69(6): 835-837; 1978.

The synthesis and carcinogenicity of 4-(N-hydroxy-N-methylamino)-quinoline 1-oxide (N-Me-4-HAQO) were investigated. The compound, which consists of the quinoline 1-oxide moiety of 4-nitroquinoline 1-oxide and the N-hydroxy-N-methylamino group of N-hydroxy-N-monomethylaminoazobenzene, was synthesized by treatment of 4-chloroquinoline 1-oxide with N-methylhydroxylamine. The compound was fairly stable. Following 10 weekly sc injections (0.15 or 1.5 mg each) into 5-wk-old male ddY mice, the following palpable tumors were induced at the site of injection within 105 to 390 days: fibrosarcomas in 13 of 22 animals, an unclassified sarcoma in 1 animal, and a squamous cell papilloma in 1 animal. (9 refs)

- 79-0809 Ethoxyquin Feeding to Rats Increases Liver Microsome-catalyzed Formation of Benzo(a)pyrene Diol Epoxide-DNA Adduct.** (Eng) Kahl, R. (Dept. Pharmacology, Univ. Mainz, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany); Deckers-Schmelzle, B.; Klaus, E. *Biochem Biophys Res Commun* 85(3): 938-945; 1978.

The effect of feeding ethoxyquin (EQ) on the liver microsome-catalyzed formation of benzo(a)pyrene (BP) diol epoxide-DNA adducts was studied in vitro. The microsomes were prepared from male Sprague-Dawley rats that had received 0.5% EQ in the diet for 14 days. Calf thymus DNA was incubated with liver microsomes in the presence of 6 μ M ³H-BP. Sephadex LH 20 chromatography revealed that the formation of the benzo(a)pyrene 7,8-diol-9,10-epoxide-DNA nucleoside adduct was increased threefold by feeding 0.5% EQ. Microsomal epoxide hydratase activity was also enhanced by a factor of three, but aryl hydrocarbon hydroxylase activity was not induced. A threefold increase in the diol epoxide-DNA adduct was also found when liver microsomes from animals treated with EQ plus 3-methylcholanthrene (3-MC) were used, compared with microsomes from animals treated with 3-MC only. The main chromatographic peak formed by microsomes from 3-MC-treated rats, which contained DNA adducts of secondary BP phenol metabolites, was reduced when the animals had received EQ. Increased formation of the diol epoxide adduct was not an expected finding for a substance that reportedly reduces tumor induction by BP. However, the reduction in the formation of DNA adducts of secondary BP phenol metabolites may be related to the protective action of EQ. (25 refs)

- 79-0810 Effects of Various Chemical Agents on Sister Chromatid Exchanges, Chromosome Aberrations, and DNA Repair in Normal and Abnormal Human Lymphoid Cell Lines.** (Eng) Shiraishi, Y. (Dept. Anatomy, Kochi Medical Univ., Kochi 780, Japan); Sandberg, A. A. *J Natl Cancer Inst* 62(1): 27-35; 1979.

The effects of various chemical agents on cell lethality, chromosome aberrations, sister chromatid exchanges (SCE), and DNA repair were studied using cell lines derived from normal human male lymphocytes and from a patient with chronic lymphocytic leukemia (CML, line SN1029). Compared with the normal cells, SN1029 cells were more sensitive to the lethal effects of 4-nitroquinoline 1-oxide (4-NQO), methyl methanesulfonate (MMS), ethyl methanesulfonate (EMS), mitomycin C (MMC), daunomycin (DM), bleomycin, and cytosine arabinoside, but not to the lethal effects of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). MMC also increased the frequency of SCE in SN1029 cells but did not increase the frequency of chromosome breakages. The other agents did not increase the SCE frequency, although they did increase chromosome aberrations. Unscheduled DNA synthesis (USD) was examined following UV irradiation and chemical treatment for 90 min at 6.0 μ g/ml (experiment 1) or for 48 hr at 0.003-6.0 μ g/ml (experiment 2). USD

occurred after treatment with 4-NQO, EMS and MNNG but not after treatment with MMC in experiment 1. USD did not occur after any treatment in experiment 2. The repair level did not differ between normal and SN1029 cells exposed to UV-radiation and 3-NQO, EMS, or MNNG. The results indicate the SCE and excision repair are not closely linked and that the SCE sensitivity and cell death of the CLL line are independent of the quantitative capacity for excision repair. (19 refs)

- 79-0811 Kinetics of DNA Repair Synthesis in Human Fibroblasts Induced by Chemical Carcinogens and Ultraviolet Light (Meeting Abstract).** (Eng) Levinson, J. W. (Michigan State Univ., East Lansing, MI, 48824); Maher, V. M.; McCormick, J. J. *Biophys J* 25(2, part 2): 154a; 1979. (no refs)

- 79-0812 Metabolic Pathways of the N-Substituted Naphthalenes: Their Relationship to Mutagenicity and Carcinogenicity (Meeting Abstract).** (Eng) Benkendorf, C. A. (Univ. Michigan, Ann Arbor, MI, 48104). *Diss Abstr Int B* 39(6): 2723; 1978. (1 ref)

- 79-0813 Polarographic Determination of Some Carcinogenic Aminoazobenzenes.** (Eng) Carruthers, C. (Orchard Park Lab., Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263). *Mikrochim Acta* 2(5/6): 463-472; 1978.

Polarography was applied to the quantitative analysis of 14 carcinogenic and noncarcinogenic aminoazobenzenes in ethanol-buffer solns. Plots of diffusion current vs concentration gave straight lines with different slopes, so that this method can be used for the quantitative analysis of any of the compounds tested. As the pH increased, the diffusion current decreased. Only N'-methyl-4'-amino-N-methyl-4-aminoazobenzene could be determined in the presence of any of the ring-substituted aminoazobenzenes on the basis of half-wave potential. There was no apparent relationship between structure and half-wave potential or between half-wave potential and carcinogenicity of the ring-substituted aminoazobenzenes. (17 refs)

- 79-0814 An Evaluation of a Polyurethane for Use as a Medical Grade Plastic.** (Eng) Darby, T. D. (Travenol Labs., Inc., Morton Grove, IL, 60053); Johnson, H. J.; Northup, S. J. *Toxicol Appl Pharmacol* 46(2): 449-453; 1978.

The mutagenic potential of 4,4'-methylenedianiline (MDA), an aromatic amine analog of 4,4'-diphenylmethane diiso-

cyanate (MDI), was tested in the Ames' mutagenicity assay using *Salmonella typhimurium* test strains TA98, TA100, TA1535, TA1537, and TA1538. MDI is a constituent of a new polyurethane developed for use as blood bag material, and it yields MDA when it is autoclaved in aqueous soln for 2 or 5 hr. MDA (50 or 150 μ g) was incubated with the bacteria in the presence or absence of an S-9 liver microsome fraction from Sprague-Dawley rats. MDA was mutagenic to strains TA100 and TA98 in the presence of the S-9 mix (the number of revertants was more than double that seen in control plates), and the effect was dose-dependent. Thus, it was decided that the specific aromatic polyurethane did not have a benefit/risk ratio comparable to those established for existing blood bag materials. (11 refs)

79-0815 Testing of Twenty-one Environmental Aromatic Amines or Derivatives for Long-term Toxicity or Carcinogenicity. (Eng) Weisburger, E. K. (Carcinogen Metabolism and Toxicology Branch, NCI, Bethesda, MD, 20014); Russfield, A. B.; Weisburger, J. H.; Boger, E.; Van Dongen, C. G.; Chu, K. C. *J Environ Pathol Toxicol* 2(2): 325-356; 1978.

Twenty-one aromatic amines and derivatives were tested for long-term toxicity following dietary administration to male Charles River rats and male and female HaM/ICR mice. 2,4-Toluenediamine, o-phenylenediamine, o-toluidine, 2,4,6-trimethylaniline, 2,4,5-trimethylaniline, 2,5-xylidine, and 1-chloro-2-nitrobenzene produced tumors in all three animal models, whereas p-toluidine, 4-chloro-o-toluidine, and 1-chloro-4-nitrobenzene were carcinogenic only in the mice. 4-Chloro-4'-aminodiphenyl ether affected the rats and female mice, but there was no consistent dose response. 2,5-Dimethoxy-4'-aminostilbene was carcinogenic in the rats but had only a questionable action in male mice; it was noncarcinogenic in female mice. 3,3',4,4'-tetraaminobiphenyl was carcinogenic in male mice, but its effect in the rats was borderline; it was noncarcinogenic in female mice. 2,4,6-Trichloroaniline was carcinogenic in male mice but not in rats, tetrafluoro-m-phenylenediamine was somewhat less carcinogenic in male mice and noncarcinogenic in the rats and in female mice, and m-toluidine showed only questionable activity (in male mice). 2,4-Xylidine was carcinogenic in female mice but not male mice or rats; 2,4,6-trimethylaniline caused hepatic cirrhosis in rats only and no tumors in rats or mice. m-Phenylenediamine, 2,4-dinitrochlorobenzene benzoquinamine, and dicyclopentadiene dioxide were inactive in both species. (31 refs)

79-0816 Air Sampling and Analytical Method for 4,4'-Methylenebis(2-chloroaniline). (Eng) Rapaport, S. M. (Sch. Public Health, Univ. California, Berkeley, CA, 94720); Morales, R. *Anal Chem* 51(1): 19-23; 1979.

A sampling/analytical method for determining airborne exposures of individuals to the carcinogen 4,4'-me-

thylenebis(2-chloroaniline) (MOCA) was developed. The sampler uses a filter to collect particulate MOCA and a bed of silica gel to remove the vapors. MOCA is analyzed by a high-pressure liquid chromatography equipped with a UV photometer (254 nanometers). The method allows quantitation of 3 nanograms of MOCA corresponding to 0.15 μ g/sample. (14 refs)

79-0817 Lifespan Carcinogenicity Studies with Hexachlorophene in Mice and Rats. (Eng) Rudali, G. (Equipe de Recherche 190 du C.N.R.S., Fondation Curie, 26 rue d'Ulm, Paris, France); Assa, R. *Cancer Lett* 5(6): 325-332; 1978.

Hexachlorophene (HCP) was tested for carcinogenicity in lifetime feeding studies in male Sprague-Dawley rats fed a protein- and vitamin-deficient diet and in C57Bl and XVII/G mice fed a complete diet. Rats received a daily HCP dose of approx 1.5 mg/rat and mice, approx 0.45 mg/mouse. Lifespan and survival rates were similar in treated and control groups. No significant carcinogenic effects were observed in rats or mice during the 2-yr study period. In XVII/G mice injected at birth (0.05, 0.05, and 0.1 mg HCP/animal sc on days 1, 2, and 8 of life) or receiving HCP in the mother's milk (0.5 mg HCP/nursing animal for 20 days), the incidence of tumors was not statistically increased. One of the males injected at birth developed a nonmalignant hepatoma, and three of the males that received HCP during nursing developed liver tumors, one of which was an adenocarcinoma. None of the untreated mice developed hepatomas. No carcinogenic effect was observed in (C57Bl x C3H) F₁ hybrid mice that received HCP transplacentally (0.5 mg/pregnant mouse on gestation days 16 and 18). It is concluded that HCP is not carcinogenic for rodents. (16 refs)

79-0818 Carcinogenesis of Hexachlorobenzene in Mice. (Eng) Cabral, J. R. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NE, 68105); Mollner, T.; Raitano, F.; Shubik, P. *Int J Cancer* 23(1): 47-51; 1979.

Long-term experiments on the carcinogenicity of hexachlorobenzene (HCB) were carried out in outbred Swiss mice. The animals received HCB at 50 ppm in the diet for 120 wk, 100 ppm for 106 wk, 200 ppm for 101 wk, or 300 ppm for 15 wk. Survival was reduced after the 30th wk in mice given 200 and 300 ppm HCB. The incidence of liver-cell tumors was increased in mice fed more than 50 ppm; the percentages of liver tumor-bearing animals in the control, 50-ppm, 100-ppm, 200-ppm, and 300-ppm groups was 0%, 0%, 10%, 25%, and 5%, respectively. Most liver-cell tumors were first observed between wk 50 and 99. Lymphoma incidence was 35% in controls, 48% in animals fed 50 ppm HCB, 21% in those fed 100 ppm, 11% in those fed 200 ppm, and 25% in those fed 300 ppm. The low tumor incidence in mice fed HCB, particu-

larly those fed 200 ppm, probably reflects the fact that these animals had the shortest life span; the av time of death for mice with lymphomas following treatment with 200 ppm HCB was 56 wk, in comparison with 86 wk in controls. The incidence of lung tumors was higher in controls than in the treated groups, but the multiplicity (nodules/mouse) was approximately the same in all groups. The results show that concentrations of 100 ppm HCB or more in the diet induce liver-cell tumors in mice, which confirms the results of previous studies. (14 refs)

- 79-0819 Determination of Benzene Concentrations in Work Areas by Gas Chromatography.** (Rum) Matei, L. (Institutul de Igiena si sanatate publica, Bucharest, Romania); Pasat, V. *Rev Ig (Ig)* 27(3): 285-288; 1978.

A gas chromatographic method for the separation and quantitative determination of benzene in work areas is described. Benzene is adsorbed from the air on activated carbon. The method is simple, rapid, specific, and highly sensitive (1 nanogram/ μ l). (30 refs)

- 79-0820 Determination of Benzene Level in Blood.** (Rus) Pinigina, I. A. (A. N. Sysin Inst. General and Communal Hygiene, Moscow, USSR); Mal'tseva, N. M. *Gig Sanit* (12): 67-71; 1978.

Disadvantages of the analysis of biologic specimens by head space chromatography are discussed briefly, and a modified method of determining microquantities of benzene in the blood of experimental animals is described. The sensitivity of the assay was 0.01 μ g/0.5 ml of blood; the duration of analysis ranged from 10 to 15 min. (6 refs)

- 79-0821 Contamination from Feeding Volatile Test Chemicals.** (Eng) Sansone, E. B. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21501); Losikoff, A. M. *Toxicol Appl Pharmacol* 46(3): 703-708; 1978.

Experiments demonstrating that workers, animals, and the environment may be exposed to the vapors of chemicals added to granular diets are presented. When 1,3,5-trichlorobenzene (TCB), a moderately volatile solid, was added to the granular diet of rats at 5 g TCB/kg diet, vapor-phase TCB was detected in room air (30 ppb), cage air (1-130 ppm), and air samples obtained in the clean and return corridors outside the room. About 4 g/day were exhausted to the atmosphere. (12 refs)

- 79-0822 Metabolic Activation of 2,4-Diaminoanisole, a Hair-Dye Component--II. Role of Cytochrome**

P-450 Metabolism in Irreversible Binding In Vitro. (Eng) Dybing, E. (Dept. Environment Toxicology, Natl. Inst. Public Health, Oslo 1, Norway); Aune, T.; Nelson, S. D. *Biochem Pharmacol* 28(1): 43-50; 1979.

The possibility that cytochrome P-450 metabolism leads to the formation of reactive forms of 2,4-diaminoanisole (2,4-DAA) that bind irreversibly, to protein and other macromolecules was investigated. Incubation of rat liver microsomes with 3 H-2,4-DAA in the presence of NADPH and O_2 led to the formation of products irreversibly bound to microsomal protein. The binding was inhibited by a $CO:O_2$ atmosphere and by an antibody against NADPH cytochrome c reductase. Addition of cytochrome P-450 inhibitors such as SKF 525-A and metyrapone also inhibited binding, whereas α -naphthoflavone slightly stimulated binding rates, β -naphthoflavone had no effect. Pretreatment of animals with phenobarbital increased binding rates to 175% of controls. Experiments with 3 H- and 14 C-ring-labeled 2,4-DAA indicated some loss of 3 H, which was confirmed by isolation of labile 3 H. Substitution of the H's in the methyl group with deuterium led to increases in both binding and mutagenicity of 2,4-DAA. Formation of formaldehyde and a small amount of methanol could be demonstrated during the oxidative metabolism of methyl-labeled 2,4-DAA. Addition of superoxide dismutase and ascorbic acid inhibited binding, and a small amount of irreversible binding could be demonstrated when NADPH was replaced by a xanthine-xanthine oxidase system. Microsomes from rat kidney also activated 2,4-DAA in the presence of NADPH. Irreversible binding could be shown with liver microsomal RNA in vitro but not with exogenous DNA. A tentative scheme involving aromatic hydroxylation, oxidative demethylation, and N-hydroxylation for the microsomal metabolism of 2,4-DAA is proposed. (26 refs)

- 79-0823 Metabolic Activation of 2,4-Diaminoanisole, a Hair-Dye Component--III. Role of Cytochrome P-450 Metabolism in Irreversible Binding In Vivo.** (Eng) Dybing, E. (Dept. Environmental Toxicology, Natl. Inst. Public Health, Oslo 1, Norway); Aune, T.; Nelson, S. D. *Biochem Pharmacol* 28(1): 51-55; 1979.

The metabolism of 2,4-diaminoanisole (2,4-DAA) and the irreversible binding of this compound in vivo were studied in male Wistar rats inoculated with 3 H-2,4-DAA (10-200 mg/kg ip). There was a linear dose response of binding to liver and kidney at 4 hr after injection. No binding to liver RNA or DNA was detected. Pretreatment of animals with the cytochrome P-450 phenobarbital and β -naphthoflavone increased binding to protein in liver and kidney, but cobaltous chloride lowered binding in both organs. Irreversible binding was preferentially localized in the endoplasmic reticulum of the liver cell; considerable binding was also found in the proteins of the cytosol. Diethyl maleate pretreatment led to a 40% increase in liver binding but had no effect on kidney binding. Unbound 3 H-2,4-DAA was rapidly cleared from plasma, liver, and kidneys (peak values were

seen at 0.5 hr). Considerable amounts of irreversibly bound material could still be demonstrated in the liver and kidneys 24 hr after a 100-mg/kg dose. Some irreversibly bound radioactivity was also found in the proteins of lungs, adrenals, and blood. The effects of inducers and inhibitors of cytochrome P-450 on 2,4-DAA binding in vivo suggest that it is dependent on cytochrome P-450 metabolism, as has been shown in vitro. The relevance of the finding of irreversible binding of 2,4-DAA to hepatic protein in vivo is uncertain. (16 refs)

- 79-0824 Analysis of Biliary and Urinary Metabolites of 3'-Methyl-4-(dimethylamino)azobenzene in Rats.** (Eng) Mori, Y. (Gifu Coll. Pharmacy, Mitahora-higashi 5-6-1, Gifu 502, Japan); Hori, T.; Toyoshi, K. *Gann* 69(6): 757-762; 1978.

Metabolites of 3'-methyl-4-(dimethylamino)azobenzene (3'-Me-DAB) in rat bile and urine were analyzed quantitatively by a radiotracer technique. ³H-3'-Me-DAB (45 mg/kg in cottonseed oil) was administered to male Wistar rats by stomach tube. Biliary and urinary metabolites collected within 24 hr after treatment were hydrolyzed with β -glucuronidase/aryl-sulfatase. The hydrolyzed metabolites were then extracted with chloroform or separated by chromatography on Amberlite XAD-2 using methanol as a solvent. The metabolites in the chloroform or methanol eluates were identified by reverse isotope dilution, before or after they were separated by thin-layer chromatography. N-Demethylated, aryl hydroxylated, and azo-reduced metabolites were detected in the bile, in addition to products oxidized at the ring methyl group (new metabolites). On the other hand, metabolites retaining the azo-linkage were the scarcely detected in urine, in which 3-aminobenzoic acid and 3-amino-6-hydroxytoluene and their N-acetylated products were the major metabolites. These results indicate that the metabolism of 3'-Me-DAB in the rat involves oxidation of the ring methyl group. The significance of the ring methyl group to the carcinogenicity of aminoazo dyes is discussed. (9 refs)

- 79-0825 Alpha-Fetoprotein During Chemically Induced Hepatocellular Carcinoma in Rats.** (Eng) Abraham-Inpijn, L. (Dept. Internal Medicine, Univ. Hosp. Wilhelmina Gasthuis, Amsterdam, Netherlands). *Trop Geogr Med* 30(2): 227-234; 1978.

When male Wistar rats were fed the hepatocarcinogens 3-methyl-4'-(dimethylamino)azobenzene or aflatoxin B₁, α -fetoprotein (AFP)-positive sera were found in the tumor-induction phase (around 50 days). At this time, the liver showed acute liver cell necrosis but no malignant changes, and the AFP level correlated with the degree of necrosis. The presence of AFP during induction was followed by a high frequency of liver tumors in later phases. The AFP concen-

tration in the tumor phase was not related to tumor histology, but was related to the degree of cirrhosis. (33 refs)

- 79-0826 Metabolism and Mutagenicity of Styrene.** (Eng) Watabe, T. (Lab. Drug Metabolism and Toxicology, Dept. Hygienic Chemistry, Tokyo Coll. Pharmacy, Hachioji-shi, Tokyo, Japan); Isobe, M.; Sawahata, T.; Yoshikawa, K.; Yamada, S.; Takabatake, E. *Scand J Work Environ Health* 4(Suppl. 2): 142-155; 1978.

The mutagenicity of styrene (SR) toward *Salmonella typhimurium* was determined in the presence and absence of a liver supernatant fraction obtained from Wistar rats pretreated with 3-methylcholanthrene (3-MC), phenobarbital (PB), or polychlorinated biphenyls (PCB) and fortified with an NADPH-generating system (S-9 mix). In some assays, the S-9 mix was preincubated in the presence of 1 mM 3,3,3-trichloropropene oxide (TCPO), a microsomal epoxide hydrolase inhibitor. SR was mutagenic toward *S. typhimurium* strain TA100 after activation with S-9 mix containing fractions from 3-MC- or PB-treated rats + TCPO. No mutagenicity was observed when TCPO was omitted or when fractions from PCB-treated rats were used. The S-9 fraction from 3-MC-treated rats was more effective than that from PB-treated animals. The mutagenicity of phenylloxirane (PO), a primary metabolite of SR, was decreased markedly by the S-9 mix, and this decrease was partially inhibited by TCPO. Gas chromatographic (GC) data indicated that PO could not account for the mutagenicity induced by the hepatic activation of SR, since the sums of PO and its hydrolysis product 1-phenyl-1,2-ethanediol (PE: formed from SR during incubation with S-9 \pm TCPO) were much smaller than the amount that induced mutagenesis. GC data also showed that PCB were the most potent inducers of hepatic monooxygenase, which catalyzes the conversion of SR to PO. PCB were 1.4 times as effective as 3-MC in spite of their inability to increase the hepatic activation system for SR mutagenicity. Therefore, at least one more unknown active metabolite with an epoxide structure may be present. Evidence is presented for the NADPH-dependent covalent binding of SR to rat liver microsomal protein. This binding was increased by TCPO in vitro and by PB pretreatment of rats in vivo and decreased by pretreatment of rats with carbon tetrachloride. (38 refs)

- 79-0827 Effects of Long-term Oral Administration of Styrene to Mice and Rats.** (Eng) Ponomarev, V. (International Agency Res. Cancer, Lyon, France); Tomatis, L. *Scand J Work Environ Health* 4(Suppl. 2): 127-135; 1978.

In long-term carcinogenicity tests, styrene (SR) monomer was given po to female O₂₀ mice (1,350 mg/kg) C57Bl mice (300 mg/kg), and BD IV rats (1,350 mg/kg) on gestation day 17, and their offspring were treated weekly with SR by stom-

ach tube from the time of weaning throughout their life-span. Weekly doses were 1,350 mg/kg for O₂₀ mice, 300 mg/kg for C57Bl mice, and 500 mg/kg for BD IV rats. Following continuous SR administration for > 100 wk, there was a significantly increased and earlier incidence of lung tumors in male and female O₂₀ mice compared with olive oil-treated controls. Histologically, the lung tumors were adenomas or adenocarcinomas, and the proportion of benign and malignant lung tumors was similar in the various groups. SR was severely toxic to O₂₀ mice, particularly in the liver, and it shortened the life-span considerably. Tumor incidence in C57Bl SR-treated mice was not significantly different from that seen in controls; there was a slightly increased incidence of liver tumors in males. Although total tumor incidence was also not significantly different from that of controls, BD IV rats developed a few tumors not ordinarily seen in control animals. These consisted of three stomach tumors and three neurogenic tumors. The results provide weak evidence of the carcinogenicity of SR in O₂₀ mice when given at a high dose level. (7 refs)

- 79-0828 Phenacetin Studies (Letter to Editor).** (Eng) Cuatrecasas, P. (Wellcome Res. Lab., Burroughs Wellcome Co., Research Triangle Park, NC, 27709). *Ann Intern Med* 203(4375): 6-7; 1979.

Several long-term studies of the carcinogenicity of phenacetin in laboratory animals are cited to demonstrate that there is no positive evidence of tumor induction by this compound. Hence, the recent inclusion of phenacetin in a list of "chemicals known to be carcinogenic in man" introduces an error and gives wide circulation to misinformation. (3 refs)

- 79-0829 Effects of Dietary Butylated Hydroxytoluene and Phenobarbital on the Activities of Ornithine Decarboxylase and Thymidine Kinase in Rat Liver and Lung.** (Eng) Saccone, G. T. (Dept. Food Microbiology and Toxicology, Food Res. Inst., Univ. Wisconsin-Madison, Madison, WI, 53706); Pariza, M. W. *Cancer Lett* 5(3): 145-152; 1978.

The hypothesis that butylated hydroxytoluene (BHT) and phenobarbital (PB) stimulate increases in ornithine decarboxylase (ODC) activity as an essential part of their mode of action in inducing hyperplasia in rat liver was investigated. Male Sprague-Dawley rats were entrained to an inverted 12-hr dark/12-hr light cycle, with food (60% casein diet \pm 0.5% BHT or 0.05% PB) being available during the first 2 hr of the dark period. A characteristic diurnal oscillation in hepatic ODC activity was noted in control animals under these conditions. BHT and PB had no appreciable effect on this activity during the first 3 days of feeding. Hepatic thymidine kinase (TK) activity, however, was stimulated 4-10 times at 3 days. In lungs from the same animals, ODC and TK activities were unchanged. On the third day of BHT feeding,

the incorporation of ³H-thymidine into liver DNA was stimulated in a manner that correlated well with the observed increase in TK activity during most of this day. In lung DNA, ³H-thymidine incorporation was decreased (approx 50% of controls) after BHT feeding. The effects of BHT were transitory, as on day 22 no differences were found between BHT-fed and control rats with respect to the biochemical parameters studied. It is concluded that if there is a critical and rate-limiting hepatic growth "step" actuated by BHT and PB, it cannot be ODC. (15 refs)

- 79-0830 Hydantoin-induced Lymphadenopathies and Lymphomas.** (Eng) Rausing, A. (Univ. Inst. Pathology General Hosp., S-21401 Malmo, Sweden). *In: Recent Results Cancer Res* 64: 263-264; 1978.

In light of the accumulating evidence that hydantoin derivatives used as anticonvulsants (AC's) are related to the development of lymphadenopathies and malignant lymphomas, the records of the Swedish Adverse Drug Reaction Committee were investigated. Between 1967 and 1977, nine cases of lymph node (LN) complications in AC users were identified, three of which were on diphenylhydantoin (DPH), three on mephenetoin (MPT), and three on carbamazepine (CAP). During this time, the number of epileptics in Sweden was approx 40,000. Apparently, LN enlargement in patients taking AC's is rare. CAP has not previously been reported as a cause of LN enlargement, but in view of its immunosuppressive effect similar to that of the hydantoins, such a reaction may well exist. In another study, the clinical records of patients with malignant lymphoma and Hodgkin's disease were examined for AC use at the Institute of Pathology, Malmo, Sweden. Among the 451 records examined, 3 patients with immunoblastic histiocytic lymphoma had taken these drugs (DPH, MPT, and CAP, respectively) and 1 patient with well-differentiated lymphocytic lymphoma had taken DPH. Although this frequency is not high, there is a suggestion of a true increased risk, especially in the immunoblastic group. (5 refs)

- 79-0831 Hydantoin-induced Lymphadenopathies and Lymphomas: Experimental Studies in Mice.** (Eng) Krueger, G. R. (Labor fur Immunopathologie, Pathologisches Institut der Universitat Koln, Lindenburg, D-5000 Koln 41, W. Germany); Bedoya, V. A. *In: Recent Results Cancer Res* 64: 265-270; 1978.

Diphenylhydantoin (DPH) was administered (6 mg/100 g in liquid diet) to female mice of three strains: C3Hf, resistant to lymphoma development; C57BL, which show a low spontaneous incidence of lymphomas and leukemias; and SJL/J, which exhibit a high spontaneous incidence of malignant lymphomas. Groups of mice were autopsied every 8 wk beginning 6 wk after initiation of treatment, and tissues were studied with histological techniques, immunofluorescence,

and electron microscopy. No C3Hf mice developed tumors, whereas 12% of C57BL (vs 4% of controls) and 25% of SJL/J mice (vs 0% of controls) developed thymic lymphoblastic lymphomas. The tumor cells were occasionally slightly positive for acid phosphatase; no B- or T-cell markers were demonstrated. Tumors were successfully transplanted sc into isogenic mice in 80% of the cases. Electron microscopy showed the tumor cells to be predominantly lymphoblastic in nature, with widened perinuclear cisternae, dilated endoplasmic reticulum, and mitochondria showing loss of cristae and occasional incorporation of ribosomelike material as well as myelinic structures. No virus-related cytopathic changes or intracellular C-type viral particles were noted. It appears that DPH is effective in producing atrophic and reactive changes in immunocompetent tissues with coincident reticulohistiocytic hyperplasia. (14 refs)

79-0832 Monoclonal Gammopathy and Subsequent Multiple Myeloma in a Patient on Chronic Diphenylhydantoin Therapy. (Eng) Matzner, Y. (Dept. Hematology, Hadassah Univ. Hosp. and Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel); Polliack, A. *Isr J Med Sci* 14(12): 1265-1267; 1978.

The case of a patient who developed monoclonal gammopathy followed by classical multiple myeloma while receiving chronic diphenylhydantoin (DPH) therapy is presented. The patient, a 54-yr-old man, had been receiving DPH for 20 yr for the treatment of epilepsy. At the time of the first hospitalization, hypertension, hypertensive retinopathy, left hemiparesis, and mild axillary lymphadenopathy were present. RBC sedimentation rate was raised to 100 mm (West), and there was proteinuria of 2-10 g/day. Serum protein electrophoresis revealed the presence of a paraprotein between the β and γ regions, which constituted 29% of the total protein. Eight months later, while the patient was still receiving DPH, he was hospitalized because of cellulitis, septic shock, bone pain, and wt loss. Serum and urine immunoelectrophoresis revealed the presence of an IgG- γ paraprotein. The diagnosis of multiple myeloma was made at this time. Continuous melphalan therapy (2 mg/day) was started, and diphenylhydantoin therapy was discontinued. The patient remains in remission after 2 yr of follow-up. The authors suggest that periodic clinical examination and repeated serum electrophoresis be performed in patients receiving diphenylhydantoin therapy. (24 refs)

79-0833 Metabolic Conversion of 1- and 2-Nitronaphthalene to 1- and 2-Naphthylamine in the Rat. (Eng) Johnson, D. E. (Hoechst-Roussel Pharmaceuticals, Inc., Somerville, NJ, 08876); Cornish, H. H. *Toxicol Appl Pharmacol* 46(3): 549-553; 1978.

The possible conversion of 1- and 2-nitronaphthalene (1- and 2-NN) to the corresponding naphthylamines was studied fol-

lowing ip injection of 100 mg/kg 1- or 2-NN into the adult male Sprague-Dawley rats. The gas-liquid chromatographic retention times and mass fragmentation spectra of the 2-naphthylamine isolated as a metabolite of 2-NN and the 1-naphthylamine isolated as a metabolite of 1-NN were identical to those of the 2- and 1-naphthylamine standards, respectively. Evidence that the metabolism of NN's leads to the formation of the corresponding amines, one of which (β -naphthylamine) is a known carcinogen, suggests that human exposure to these compounds should be minimal. It also points out the important role of metabolic studies in the evaluation of potential chemical toxicity and suggests a critical reevaluation of compounds whose metabolism by known pathways could lead to the in vivo formation of carcinogenic compounds. (16 refs)

79-0834 In Vitro Reductive Metabolism of N-Nitrosodibenzylamine: Evidence for New Reactive Intermediates. (Eng) Gal, J. (Dept. Pharmacology, Div. Clinical Pharmacology: C237, Sch. Medicine, Univ. Colorado Medical Center, Denver, CO, 80262); Estin, C. D.; Moon, B. J. *Biochem Biophys Res Commun* 85(4): 1466-1471; 1978.

N-Nitrosodibenzylamine (DBNA: 1.0 or 0.10 mM) was incubated anaerobically with whole-liver homogenates from seven rabbits (6 male, 1 female) for 30 min, and organic extracts of the incubation products were analyzed by gas chromatography and mass spectrometry. One of the incubation products was identified as bibenzyl. Incubation of DBNA with whole blood under the conditions used for liver preparations gave no detectable bibenzyl. No bibenzyl was obtained when 1,1-dibenzylhydrazine or dibenzylamine was used as substrate. The formation of bibenzyl from DBNA is the result of a 2-electron reduction of the substrate to 1-hydroxy-2,2-dibenzylhydrazine, an unstable compound that breaks down to bibenzyl and nitrogen. The metabolic 2-electron reduction of nitrosamines results in highly reactive intermediates such as N-hydroxyhydrazines and diazenes, some of which are known to react with nucleophiles. (15 refs)

79-0835 Carcinogenicity Studies on Different Diarylide Yellow Pigments in Mice and Rats. (Eng) Leuschner, F. (Laboratorium für Pharmakologie und Toxikologie, Hamburg, W. Germany). *Toxicol Lett* 2(5): 253-260; 1978.

The carcinogenicity of three pure diarylide yellow pigments and one contaminated with 3,3'-dichlorobenzidine (DCB) was tested in mice (NMRI, Ivanovas) and rats (Sprague-Dawley, Ivanovas). The pigments were administered in the feed at concentrations of 0.1%, 0.3%, and 0.9% (av 215, 650, and 1,960 mg/kg/day in mice and 68, 205, and 630 mg/kg/day in rats) for 104 wk. A fifth diarylide pigment was given to five rabbits in a single po dose of 50 mg/kg. Metabolism to DCB or 3,3'-dimethylbenzidine (DMB) was determined by

urinalysis after 6 and 23 mo in the mice and rats and after 48 and 72 hr in the rabbits. Mice and rats tolerated the pigments up to the 0.9% dietary level; there were no adverse effects on growth, food intake, health condition, survival, or the histological appearance of major tissues and organs, even when DCB (20 ppm) was added to the one pigment. Neither DCB nor DMB was detected in urine samples of mice, rats, or rabbits; the analytical methods were sensitive to concentrations as low as 3 µg/10 ml urine. It is unlikely, therefore, that these pigments will present a health hazard or an increased carcinogenic risk to the population exposed via manufacturing and usage as long as the contamination level of DCB and DMB is kept under control. (21 refs)

79-0836 Uptake of Glucuronides into Isolated Hepatocytes and Their Effects on Glucuronide and Sulfate Conjugation. (Eng) Norling, A. (Dept. Forensic Medicine, Karolinska Institutet, S-104 01 Stockholm, Sweden); Andersson, B.; Berggren, M.; Moldeus, P. *Acta Pharmacol Toxicol (Kbh)* 43(4): 311-317; 1978.

Uptake studies, using radioactive 4-nitrophenyl glucuronide and phenolphthalein glucuronide, have demonstrated the ability of these glucuronides (GCN) to enter isolated rat hepatocytes. However, the intracellular distribution and cellular binding of the two GCN's differed. These differences may be due to their varied mol wts of lipophilicity. The differences in cellular binding of the GCN's are also reflected in their ability to interfere with uridine diphosphate-glucuronosyltransferase activity. (16 refs)

79-0837 Possible Carcinogenetic Properties of a New Chromogen, Dicarboxydine (γ,γ' -3,3'-Benzidine Dioxidybutyric Acid), Tested in Rats and Mice. (Eng) Pliss, G. B. (Lab. Carcinogenic Agents, Petrov Res. Inst. Oncology, 68 Leningradskaya St., Pesochny-2, Leningrad 188646, USSR); Volfson, N. I. *J Natl Cancer Inst* 62(2): 301-304; 1979.

The carcinogenic potential of γ,γ' -3,3'-benzidinedioxidybutyric acid (dicarboxydine:DCD) was tested in 208 white noninbred rats and 127 CC57BR mice. Rats were injected sc with 35 or 45 mg DCD in sunflower oil 1x/wk or fed 20 mg in the diet 5x/wk, all for 24 mo. Mice received 4 mg DCD or 3 mg dianisidine dihydrochloride (DAZ) sc 1x/wk or 3 mg DCD in the diet 5x/wk, all for 18.5 mo. Although 21/99 surviving rats developed tumors, there was no significant difference in tumor incidence between treated and control groups. The av latent period in the treated rats was always > 18 mo. Only single cases of tumors occurred at sites other than those in the four control animals, and they were in the bladder, prostate gland, uterine body, and other organs. Four rats developed sarcomas, but only at the injection site. Of 72 surviving mice, 18 developed tumors, 9 of which were liver hemangiomas and 2 lung adenomas. Three control mice de-

veloped tumors. Correlation of the results obtained in the experimental and control groups of mice and the oncogenic characteristics of CC57BR mice, led to the conclusion that DCD and DAZ have no carcinogenic effects in these animals. The longer period of tumor induction in treated animals, the paucity of tumors after po administration in rats, and the lack of carcinogenic effect in mice indicate that DCD is of dubious or negative carcinogenicity. (9 refs)

79-0838 Detection of the 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Receptor in Rat Liver by Isoelectric Focusing in Polyacrylamide Gels. (Eng) Carlstedt-Duke, J. (Dept. Chemistry, Karolinska Institutet, S-104 01 Stockholm 60, Sweden); Elfstrom, G.; Snochowski, M.; Hogberg, B.; Gustafsson, J. A. *Toxicol Lett* 2(6): 365-373; 1978.

Isoelectric focusing in polyacrylamide gels was used to detect the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) receptor in rat liver. Both serum and liver cytosol from young male Sprague-Dawley rats contained a dextran-coated charcoal-resistant (^3H)-TCDD-binding protein, the serum-binding protein having a larger capacity than the cytosol-binding protein. The serum-binding protein focused as a sharp peak with pI 5.7 to 5.8, whereas the cytosol-binding protein focused as several peaks with variable pI's. The cytosol TCDD receptor could be completely separated from the serum binder by trypsin treatment and isoelectric focusing. The binding of (^3H)-TCDD to the receptor was competed for by 2,3,7,8-tetrachlorodibenzofuran, 3-methylcholanthrene, and β -naphthoflavone, but not by phenobarbital, pregnenolone-16 α -carbonitrile, 17 β -estradiol, testosterone, progesterone, or dexamethasone. (14 refs)

79-0839 Mutagenicity of Anthraquinone and Benzanthrone Derivatives in the Salmonella/Microsome Test: Activation of Anthraquinone Glycosides by Enzymic Extracts of Rat Cecal Bacteria. (Eng) Brown, J. P. (Dynapol, 1454 Page Mill Road, Palo Alto, CA, 94304); Dietrich, P. S. *Mutat Res* 66(1): 9-24; 1979.

The mutagenicity of 70 anthraquinones (AQ's) and 20 benzanthrone derivatives was assayed using five tester strains of *Salmonella typhimurium* and Aroclor 1254-induced rat liver microsomes. Of the 68 9,10-AQ derivatives, 28 exhibited frameshift mutagenicity with microsomal activation. The incidence of mutagenicity was even higher for phenolic AQ's (13/25) and nitro-AQ's (3/3). The most potent mutagens were of plant origin, with lucidin (1,3-dihydroxy-2-hydroxymethylanthraquinone) and its 2-ethyl ether (1,3-dihydroxy-2-ethoxymethylanthraquinone) giving the highest revertants per nanomole, 70 and 82 respectively, with strain TA100. A number of glycosides of mutagenic hydroxy-AQ's were nonmutagenic in the standard assay, but they were activated by pretreatment with cell-free sonic ex-

tracts of rat cecal bacteria. This group included alizarin-2-O- β -D-glycoside, emodin-1(8)monoglucoside, and lucidin-3-O-primveroside. Eight of the 22 benzantrones tested exhibited frameshift mutagenicity for *Salmonella*. All were substituted in the C-3 position with oxygen, nitrogen, or sulfur. The most potent of the group was 3-(4-toluidino)-benzanthrone, exhibiting about 65 revertants/nanomole in strain TA98 with microsomal activation. Benzantrones substituted solely with halogens or sulfonates were nonmutagenic. (17 refs)

79-0840 A Relationship Between Repression of Dimethylnitrosamine-demethylase by Polycyclic Aromatic Hydrocarbons and Their Shape. (Eng) Kaliszan, R. (Dept. Physical Chemistry, Medical Acad., K. Marksa 107, 80-416 Gdansk, Poland); Lamparczyk, H.; Radecki, A. *Biochem Pharmacol* 28(1): 123-125; 1979.

The quantitative relationship between the ability of polycyclic aromatic hydrocarbons (PAH) to repress the mixed-function oxidase, dimethylnitrosamine demethylase, and a parameter expressing the shape of the PAH molecules was examined. The shape parameter represents the ratio of the longer to shorter sides of the minimum rectangular envelope around the structure, drawn proportionally to atomic dimensions. Use of the shape parameter allowed satisfactory prediction of the biological activity of 23 active and 4 inactive compounds; the results were unsatisfactory for 8 compounds. However, the correlation between the shape parameter and repressor activity toward dimethylnitrosamine-demethylase generally supports a previous suggestion regarding the importance of steric fit between the PAH molecule and its cellular receptor site. (8 refs)

79-0841 Carcinogenicity of Polycyclic Aromatic Hydrocarbons Studied by SIMCA Pattern Recognition. (Eng) Norden, B. (Dept. Organic Chemistry, Inst. Chemistry, Univ. Umea, S-90187 Umea, Sweden); Edlund, U.; Wold, S. *Acta Chem Scand B* 32(8): 602-608; 1978.

The carcinogenicity of 32 polycyclic aromatic hydrocarbons was determined on the basis of a multivariate statistical analysis of 15 theoretical, unmeasured variables and 8 measured variables. A prediction of the level of carcinogenicity for the active compounds was also made. (26 refs)

79-0842 The Effect of Sample Environment on the Room-temperature Phosphorescence of Several Polynuclear Aromatic Hydrocarbons. (Eng) Bower, E. L. (Materials Science & Engineering, Univ. Florida, Gainesville, FL, 32611); Winefordner, J. D. *Anal Chim Acta* 102(1): 1-13; 1978.

The heavy-atom effect produced significant enhancement of room-temperature phosphorescence (RTP) signals for several polycyclic aromatic hydrocarbons (PAH), the hierarchy being $Tl+ > Ag+ > Pb^{2+} > Hg^{2+}$. $Tl+$ also enhanced the spectral features of emission bands. RTP was induced from PAH on both sodium acetate and filter paper sample supports. Anomalous results were obtained in a study of the effect of various gaseous environments. (40 refs)

79-0843 High Pressure Liquid Chromatographic Determination of Polynuclear Aromatic Hydrocarbons in Oysters. (Eng) Hanus, J. P. (Food and Drug Admin., 3032 Bryan St., Dallas, TX, 75204); Guerrero, H.; Biehl, E. R.; Kenner, C. T. *J Assoc Off Anal Chem* 62(1): 29-35; 1979.

Reverse-phase high-pressure liquid chromatography was used to determine 13 polynuclear aromatic hydrocarbons in oysters at the 2-ppb level. Recoveries from spiked samples generally were $> 80\%$. (15 refs)

79-0844 Clastogenic Effects of Frusemide on Human Leukocytes in Culture. (Eng) Jameela (Cytogenetics Lab., Dept. Genetics, Osmania Univ., Hyderabad 500007, India); Subramanyam, S.; Sadasivan, G. *Mutat Res* 66(1): 69-74; 1979.

The clastogenic effects of the diuretic frusemide were evaluated in human chromosomes in vitro. Cultures of WBC from normal donors were exposed to three concentrations of frusemide (0.2, 0.4, or 0.8 mg/ml) for 24 or 72 hr, and 100-110 metaphases were scored. There was a decrease in the mitotic index after both treatment times. The induction of chromosome aberrations was dose-dependent. There was a significant increase of moderate damage (gaps and breaks) and a low incidence of multiple aberrations after 24 hr exposure, but the reverse was true after 72 hr exposure. Exchanges, dicentric, and acentric were only seen after 24 hr exposure. The total percentage of aberrations was higher after 24 hr exposure. The predominance of chromatid over chromosome aberrations suggests that the drug acts during the S and G₂ phases of the cell cycle. Exchanges were significant at all doses except 0.2 mg/ml in the 24-hr test, which indicates the chromosome-breaking potential of the chemical. The absence of exchanges after 72 hr exposure may be due to their high instability. It is concluded that frusemide is capable of causing chromosome mutations. (19 refs)

79-0845 Potential Proximate Carcinogens of 7,12-Dimethylbenz(a)anthracene: Characterization of Two Metabolically Formed *trans*-3,4-Dihydrodiols (Letter to Editor). (Eng) Yang, S. K. (Dept. Pharmacology, Sch. Medicine, Uniformed Services Univ. Health Sciences, Bethesda, MD, 20014); Chou, M. W.; Roller, P. P. *J Am Chem Soc* 101(1): 237-239; 1979.

Two previous unreported metabolites of 7,12-dimethylbenz(a)anthracene (DMBA) were obtained by in vitro incubation of DMBA with rat liver microsomes and a NADPH-generating system at 37 C for 1 hr. The structure of the two resulting optically active trans-3,4-dihydrodiols was characterized in detail. Upon further metabolism, they had greater in vitro DNA-binding and mutagenic activity than their parent hydrocarbons [DMBA and 7-hydroxymethyl-12-methylbenz(a)anthracene] and therefore are potential proximate carcinogens. Multiple activation pathways may contribute to the biological activities of DMBA. (21 refs)

79-0846 The Development of a System for Organ Culture of Hamster Cheek Pouch Mucosa: Characterization of the Tissue In Vitro and Its Potential Use in the Study of Carcinogenesis. (Eng) Mock, D. (Univ. Toronto, Toronto, Ontario, Canada). *Diss Abstr Int B* 39(7): 3229B-3230B; 1979. (no refs)

79-0847 Studies on the Mechanism of 7,12-Dimethylbenz(a)anthracene Tumor-initiation in Mouse Skin: The Role of Biotransformation (Meeting Abstract). (Eng) DiGiovanni, J. (Univ. Washington, Seattle, WA, 98105). *Diss Abstr Int B* 39(6): 2763; 1978. (no refs)

79-0848 Spectroscopic Studies of In Vivo and In Vitro Nucleic Acid-Carcinogen Interactions (Meeting Abstract). (Eng) Ivanovic, V. (New York Univ., New York, NY, 10003). *Diss Abstr Int B* 39(6): 2823; 1978. (no refs)

79-0849 Mutagenicity of Polycyclic Hydrocarbons. V. Induction of Sister-Chromatid Exchanges In Vivo. (Eng) Roszinsky-Kocher, G. (Dept. Human Genetics and Anthropology, Universitätsstrasse 1, Geb. 23.12, D-4000 Dusseldorf 1, W. Germany); Basler, A.; Rohrborn, G. *Mutat Res* 66(1): 65-67; 1979.

The ability of polycyclic hydrocarbons to induce sister chromatid exchanges (SCE's) at concentrations too low to induce chromosomal aberrations was tested in 8- to 12-wk-old Chinese hamsters. The animals received two injections of test compound (450 mg/kg x 2, ip) 24 hr apart. Bone marrow chromosomes were prepared 24 hr after the second injection. The most potent SCE-inducing compound was benzo(a)pyrene (BP: 10.6 SCE's/metaphase). The av number of SCE's per cell induced by benzo(a)anthracene, benzo(b)fluoranthene, benzo(e)pyrene, phenanthrene, chrysene, and dibenzanthracene was 4.9-6.1. The number of anthracene-induced SCE's per metaphase (3.7) was not increased compared with that in controls (3.9). Only BP significantly increased the number of metaphases with chromosomal aberrations. These

results correlate with those from the *Salmonella typhimurium*/microsome mutagenicity assay and with the carcinogenicity of the test compounds. (6 refs)

79-0850 Mutagenicity and Tumor-initiating Activity of Fluorinated Derivatives of 7,12-Dimethylbenz(a)anthracene. (Eng) Huberman, E. (Biology Div., Oak Ridge National Lab., Oak Ridge, TN, 37830); Slaga, T. J. *Cancer Res* 39(2, Part 1): 411-414; 1979.

7,12-Dimethylbenz(a)anthracene (DMBA) and its 1-, 2-, 5-, and 11-fluoro derivatives were tested for mutagenicity in Chinese hamster V79 cells and skin tumor initiation in Sencar (skin-tumor-sensitive) mice. Direct mutagenicity was investigated by treating the cells for 2 days with 0.01-38 μ M of DMBA or one of its derivatives and measuring the number of ouabain-resistant mutants. None of the compounds were mutagenic in this assay, nor were they cytotoxic, as measured by the cloning efficiency of the treated cells. However, when cell-mediated mutagenicity was measured by treating V79 cells cocultivated with normal golden hamster embryonic fibroblasts, which unlike the V79 cells, can metabolize polycyclic aromatic compounds, DMBA, 1-fluoro-DMBA, 5-fluoro-DMBA, and 11-fluoro-DMBA exhibited dose-dependent mutagenicity and reduction of cloning efficiency of the V79 cells. 11-Fluoro-DMBA was as active as DMBA in these respects, whereas the 1- and 5-fluoro derivatives were 3 orders of magnitude less active than DMBA. The tumor-initiating activity of DMBA and its derivatives was tested to determine whether their metabolism to mutagenic derivatives is correlated with carcinogenicity. Single topical applications of 100 nanomoles of initiator to the mice were followed 1 wk later by applications of 12-O-tetradecanoylphorbol-13-acetate (5 μ g 2x/wk) as promoter. After 15 wk of promotion, both DMBA and 11-fluoro-DMBA had induced papillomas in 100% of the surviving mice (39/40 and 38/40 treated respectively), and there were >20 papillomas/mouse. In contrast, 1-fluoro-DMBA and 5-fluoro-DMBA were weak initiators, with only 10% and 20% tumor-bearing animals, respectively, and 2-fluoro-DMBA was inactive (only 3% tumor bearers). The results indicate that fluorination of DMBA at positions 1, 2, or 5 eliminates >99% of the mutagenic activity of DMBA for V79 cells and reduces its tumor-initiating activity by \geq 85%. (40 refs)

79-0851 The Effects of Hyaluronidase upon Tumor Formation in BALB/c Mice Painted with 7,12-Dimethylbenz(a)anthracene. (Eng) Pawlowski, A. (Clinical Science Div., Dermatology Section, Medical Sciences Bldg., Univ. Toronto, Toronto, Ontario M5S 1A8, Canada); Haberman, H. F.; Menon, I. A. *Int J Cancer* 23(1): 105-109; 1979.

The effects of hyaluronidase on 7,12-dimethylbenz(a)anthracene (DMBA) carcinogenesis were studied in BALB/c mice. Group 1 mice were painted with a 1% soln of DMBA, Group 2 mice were painted with DMBA and injected id with 0.2 ml of 0.1% hyaluronidase, and Group 3 mice were injected with physiological saline or heat-inactivated hyaluronidase and painted with DMBA. Treatments were given twice weekly for 5 wk. Compared with the mice in Groups 1 and 3, Group 2 mice showed fewer cutaneous tumors, fewer tumors per mouse, smaller tumors, a shorter latency period to appearance of tumor, and a smaller frequency distribution of the mitotic index of the skin outside the tumors. The internal organs were free of lesions except for a metastatic lesion in the lymph node of one Group 3 mouse. The data indicate that hyaluronidase decreases the carcinogenicity of topically applied DMBA. (17 refs)

79-0852 Carcinogenesis after Two Administrations of DMBA to Rats in Different Life Periods. (Rus)

P' rvanova, L. G. (Lab. Experimental Tumors, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR). *Vopr Onkol* 24(11): 96-99; 1978.

To evaluate the cumulative carcinogenic effect of transplacental and postnatal administration of 7,12-dimethylbenz(a)anthracene (DMBA), the random-bred albino female rats were divided into four groups: animals in Group 1 had transplacental exposure to DMBA (iv injection at 15 mg/kg to mothers on day 19-20 of the pregnancy), rats in Group 2 received DMBA postnatally on day 90-92, animals in Group 3 had transplacental and postnatal exposure, and rats in Group 4 served as nontreated controls. All animals were followed for 18 mo. In Group 1, 25/54 rats developed 28 tumors: 10/25 rats had tumors of the peripheral and central nervous system, 8 had tumors of the kidney, and 5 had tumors of the mammary gland (there were also leiomyomas of the small intestine, hypophyseal adenomas, glandular polyps of the uterus, hemangiopericytomas of the uterus, and hemangiosarcomas). In Group 2, 22/58 rats had 25 tumors (80% of the tumors were located in the mammary gland). In Group 3, 36/55 rats developed 56 tumors (including 19 tumors of the mammary gland, 10 neurogenic tumors, 6 kidney tumors, 2 thecafolliculomas of the ovaries, 1 adenoma of the thyroid, 2 adenomas of the hypophysis, 1 polyp of the stomach, 1 angiosarcoma of the hind extremity, and 1 lympholeukemia). Only 3/64 of the rats in Group 4 had tumors (thymoma, adenoma of the thyroid, and stromal sarcoma of the endometrium). The av life span of rats in Group 3 was 321 days, compared with 369 days in Group 1, 429 days in Group 2, and 543 days in Group 4. (12 refs)

79-0853 Effect of Deoxycholic Acid on 7,12-Dimethylbenz(a)anthracene-induced, Two-Stage Mouse Skin Carcinogenesis. (Eng) Glauert, H. P. (Food Science and Human Nutrition Dept., Michigan State Univ., East Lansing,

MI, 48824); Bennink, M. R. *Res Commun Chem Pathol Pharmacol* 22(3): 609-612; 1978.

The effect of deoxycholic acid on 7,12-dimethylbenz(a)anthracene-croton oil-induced two-stage skin carcinogenesis was investigated in CF-1 mice. Two wk following initiation with 7,12-dimethylbenz(a)anthracene (DMBA, 75 g), one of the following treatments was started: (a) 0.5% croton oil, 2x/wk; (b) 0.5% croton oil, 2x/wk, plus 1% deoxycholic acid, 3x/wk; (c) 1% deoxycholic acid, 5x/wk; or (d) acetone or ethanol vehicle, 5x/wk, as controls. The only animals to develop tumors were those that received either both DMBA initiation and croton oil promotion, or DMBA initiation and croton oil and deoxycholic acid during promotion. Mice receiving deoxycholic acid in addition to croton oil during promotion tended to develop significantly more tumors per animal than did mice receiving croton oil alone as a promoter (3.25 versus 18.11 tumors/animal at 12 wk; 10.4 versus 22.1 tumors/animal at 20 wk). In addition, the latency period for the development of tumors was shorter in those receiving deoxycholic acid plus croton oil (9.6 ± 2.3 wk) than in those receiving croton oil alone (12.0 ± 2.4 wk). Deoxycholic acid could be acting either as a tumor initiator or as a tumor promoter. The increased tumor incidence could also be caused by an increase in the toxicity or absorption of croton oil due to deoxycholic acid. (11 refs)

79-0854 Effects of Stress on DMBA-induced Tumor Growth, Plasma Corticosterone and Brain Biogenic Amines in Rats. (Eng) Bhattacharyya, A. K. (Dept. Pharmacology, Howard Univ. Coll. Medicine, Washington, DC, 20059); Pradhan, S. N. *Res Commun Chem Pathol Pharmacol* 23(1): 107-116; 1979.

The development of 7,12-dimethylbenz(a)anthracene (DMBA)-induced tumors in female Sprague-Dawley littermate rats subjected to 6 wk of (1) immobilization or (2) overcrowding plus high-pitched sound was studied. DMBA was administered to the rats intragastrically (in peanut oil), at a dose of 5 mg/wk for 5 wk. Tumor growth was markedly inhibited by both types of stress, particularly immobilization. Tumors were measurable in all nonstressed control animals, but they were measurable in only 7/10 of the overcrowded-sound-stressed animals and in only 5/9 immobilized rats. Plasma corticosterone levels were significantly higher and norepinephrine levels in the diencephalon-midbrain were significantly lower in the stressed rats compared with the nonstressed controls. There were no significant changes in the brain dopamine or serotonin levels in the stressed rats. The data indicate a possible involvement of neuroendocrine mechanisms in stress-induced inhibition of tumor growth. (20 refs)

79-0855 Inhibition of 7,12-Dimethylbenz(a)anthracene-induced Mammary Tumorigenesis in Rats by a Synthetic Protease Inhibitor, N,N-Dimethylamino-

[p-(p') - guanidinobenzoyloxy]] benzilcarbonyloxyglycolate. (Eng) Yamamura, M. (Dept. Surgery, Kansai Medical Univ., 1 Fumizoncho, Moriguchi 570, Japan); Nakamura, N.; Fukui, Y.; Takamura, C.; Yamamoto, M.; Minato, Y.; Tamura, Y.; Fujii, S. *Gann* 69(6): 749-752; 1978.

Female albino Sprague-Dawley rats were inoculated iv with 2.5 mg/100 g 7,12-dimethylbenz(a)anthracene (DMBA), and then half were fed the synthetic protease inhibitor N,N-dimethylamino- [p-(p'-guanidinobenzoyloxy)]benzilcarbonyloxyglycolate (MeDBG: 0.1% of diet) for 40 days. MeDBG depressed the induction of breast tumors (7/21 rats had tumors at 120 days vs 14/22 control rats treated only with DMBA), delayed the latent period (from 29 days to 57 days), and significantly reduced the number of tumors per rat (from 2.25 to 0.48) and the av wt of tumors per rat (from 8.25 g to 0.18 g). These findings suggest that protease may play an important role in mammary tumorigenesis. (16 refs)

79-0856 A Proposed Selective Cell Carcinogenesis in Mammary Tumors. (Eng) King, T. I. (Div. Surgical Pathology, Univ. Alabama, 619 S. 19th St., Birmingham, AL, 35233); Murad, T. M.; Waksal, S. *Am J Pathol* 93(3): 655-660; 1978.

To determine if a specific carcinogenic agent has a causal effect on the proliferation of only one cell type or on all cells in the breast secretory unit, enzyme histochemistry and electron microscopy were employed to analyze dimethylbenzanthracene (DMBA)-induced mammary tumors in female Sprague-Dawley rats and virus-associated mammary tumors in C3H/HEJ mice. The results revealed that DMBA initially affects myoepithelial cell proliferation, while the virus-associated carcinoma originated from ductular epithelial cell proliferation. Tissue culture was then used to determine if a given tumor is composed of a single cell type. Electron microscopic investigation disclosed large numbers of virus particles in the cultured murine tumors. This evidence suggests that tissue culture may be used to enhance virus recovery (following fixing for examination). It is concluded that, in the mammary gland, selective cell carcinogenesis is operative in the formation of such myoepithelial and ductular epithelial tumors. (14 refs)

79-0857 Serial Transplantation of Chemical Carcinogen-induced Mouse Mammary Ductal Dysplasias. (Eng) Medina, D. (Dept. Cell Biology, Baylor Coll. Medicine, Texas Medical Center, Houston, TX, 77030). *J Natl Cancer Inst* 62(2): 397-405; 1979.

The results are presented of serial transplantation of a group of mammary dysplasias induced by administering either 7,12-dimethylbenz(a)anthracene (DMBA) (1.0 mg ig 1x/wk for 4, 6, or 9 wk) to BALB/c mice or urethan (20 mg/mouse) for 20 wk to (C57BL x DBA)F₁ mice. The incidence of mam-

mary dysplasia remained approx the same with increasing doses of DMBA (the 4.0-, 6.0-, and 9.0-mg treatments produced 27%, 30%, and 40% incidences, respectively), and mean number of dysplasias in non-tumor bearing mice was not significantly different from those in tumor-bearing animals. Nine transplantable outgrowth lines of dysplasia were established by transplantation of the primary lesion into the cleared mammary fat pads of syngeneic mice. When followed 6-9 generations in culture, most lines exhibited a rapid decline in growth potential. The 8/9 lines that extended throughout the mammary fat pads as ductal hyperplasias did not grow subcutaneously during the first few transplant generations. Thereafter, the lines either progressed to papillomatosis or carcinomas at varying rates (usually by transplant generation 7) died out, or remained stable as atypical ductal hyperplasias. The cell lines and mammary tumors established from urethane-induced hyperplasias were ovary-dependent for tumorigenesis and tumor growth. It appears that ductal hyperplasias have high tumorigenic potential and can be classified as "high-risk" lesions. (20 refs)

79-0858 Evidence of Pancreatic Exocrine Dedifferentiation During Tumor Induction and Nonspecific Injury (Meeting Abstract). (Eng) Bockman, D. E. (Dept. Anatomy, Medical Coll. Georgia, Augusta, GA); Black, O. *Anat Rec* 193(1): 160-161; 1979. (no refs)

79-0859 Caffeine Inhibits Excision of 7-Bromomethylbenz(a)anthracene-DNA Adducts from Exponentially Growing but Not from Stationary Phase Chinese Hamster Cells. (Eng) Friedlos, F. (Chemical Carcinogenesis Div., Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks HP8 4SP, England); Roberts, J. J. *Nucleic Acids Res* 5(12): 4795-4803; 1978.

Studies were carried out to determine whether the degradation of substituted template DNA seen in 7-bromomethylbenz(a)anthracene (7-BMBA)-damaged cells growing in a potentiating concentration of caffeine could reflect the first endonucleolytic step of a subsequently abortive attempt at excision repair. The effect of subtoxic concentrations of caffeine on the excision of 7-BMBA-DNA adducts from exponentially growing and from stationary, non-DNA-replicating cultures of Chinese hamster V79-379A cells was compared. Excision of 7-BMBA-DNA adducts from the exponentially growing cultures followed logarithmic kinetics, with a half-life of approx 20 hr. Posttreatment incubation in the presence of 0.75 mM caffeine markedly reduced this loss. Caffeine caused a concomitant increase in overall DNA synthesis rate in treated exponential cultures. Excision in stationary, non-DNA-replicating cultures was slower, and caffeine did not affect this reduced rate of excision. These findings support the hypothesis that the caffeine-induced inhibition of elongation of nascent DNA on a template containing chemi-

cal lesions results in an interference with the excision repair mechanism that removes these lesions. (21 refs)

- 79-0860 Alcohol and Hamster Buccal Pouch Carcinogenesis.** (Eng) Freedman, A. (Dept. Oral Medicine and Oral Pathology, Harvard Sch. Dental Medicine, 188 Longwood Ave., Boston, MA, 02115); Shklar, G. *Oral Surg* 46(6): 794-805; 1978.

The effect of alcohol consumption on the development of leukoplakia and epidermoid carcinoma induced by dimethylbenzanthracene (DMBA) was studied in the buccal pouch of the Syrian hamster. Forty animals were divided into four equal groups: Group I had the left buccal pouch painted with 0.5% DMBA soln 3 x/wk; Group II received the DMBA treatment plus 10% alcohol added to drinking water given ad libitum; the other two groups were the untreated and the alcohol-treated controls. Animals were sacrificed after 10, 12, or 14 wk of exposure. Group II animals developed leukoplakia, dysplasia, and well-differentiated papillary epidermoid carcinoma 2 wk before Group I. The tumors, which demonstrated surface necrosis and deep invasion of underlying connective tissue, were more numerous, larger, more extensive, and histologically more anaplastic in Group II animals. Furthermore, the liver of many Group II animals demonstrated a granular degeneration of parenchymal cell cytoplasm after 12 wk. Although the specific action of alcohol in this instance is not known, this study offers further evidence of its synergistic effect in enhancing the carcinogenicity of a locally applied agent. (22 refs)

- 79-0861 Tumor Promoter Induces Sister Chromatid Exchanges: Relevance to Mechanisms of Carcinogenesis.** (Eng) Kinsella, A. R. (Departement de Biologie Moleculaire, Universite Libre de Bruxelles, B 1640 Rhode-St-Genese, Belgium); Radman, M. *Proc Natl Acad Sci USA* 75(12): 6149-6153; 1978.

The cytogenetic effects of 12-O-tetradecanoylphorbol-13-acetate (TPA) on Chinese hamster cells in vitro were studied in order to test a hypothesis of tumor promotion. TPA (10 μ l/10 ml medium) induced sister chromatid exchanges (SCE), whereas the nonpromoting derivative 4-O-methyl-TPA did not. Antipain (1 mM), leupeptin (1 mM), and fluocinolone acetonide (1 μ g/ml), inhibitors of tumor promotion, all inhibited the formation of TPA-induced SCE. Because TPA induces several gene functions, it might also induce enzymes involved in genetic recombination. Thus, the irreversible step in tumor promotion might be the result of an aberrant mitotic segregation event leading to the expression of carcinogen/-mutagen-induced recessive genetic or epigenetic chromosomal changes. (33 refs)

- 79-0862 Disturbances of Early Sea-Urchin Development by the Tumor Promoter TPA (Phorbol Ester).**

(Eng) Bresch, H. (Abteilung fur Experimentelle Pathologie, Medizinische Hochschule, D-3000 Hannover, W. Germany); Arendt, U. *Naturwissenschaften* 65(12): 660-662; 1978.

The effect of 12-O-tetradecanoylphorbol-13-acetate (TPA) on the early sea urchin embryo was studied in order to determine whether the effects of this carcinogen are similar in mammalian and nonmammalian eucaryotic cells. Sea urchin morulae were incubated with different TPA concentrations, and incubation was continued until the pluteus stage. At 10^{-7} M, TPA blocked cleavage and caused cell lysis. At 10^{-8} M, the rate of cleavage was reduced and differentiation of the embryos proceeded abnormally, resulting in anomalous gastrulae. Differentiation of the gut and skeletal development were suppressed. At 10^{-9} M, TPA had less effect on development; some gut differentiation was seen with this dose, although the skeleton was rudimentary. Development appeared normal at concentrations of 10^{-10} M or less. The noncocarcinogenic phorbol derivatives 4-O-methyl-12-O-tetradecanoylphorbol-13-acetate and 12-O-acetylphorbol-13-acetate proved to be at least 100 times less harmful to the embryo than TPA. A third experiment demonstrated that incubation with TPA for only 1 hr caused the same abnormalities as did incubation from the morula to the pluteus stage. Since the embryotoxic effects of the three phorbol derivatives apparently run parallel to their cocarcinogenic activity, the mechanisms by which the cocarcinogen acts on mammalian and embryo cells may be similar. The sea urchin embryo may represent a useful model for elucidating the molecular action of phorbol esters in cells. (9 refs)

- 79-0863 Plasminogen Activator in Chick Embryo Muscle Cells: Induction of Enzyme by RSV, PMA and Retinoic Acid.** (Eng) Miskin, R. (Lab. Chemical Biology, Rockefeller Univ., New York, NY, 10021); Easton, T. G.; Reich, E. *Cell* 15(4): 1301-1312; 1978.

The induction of plasminogen activator (PA) in differentiating chick skeletal muscle cultures by Rous sarcoma virus (RSV), phorbol myristate acetate (PMA), and retinoic acid^x was studied. Unstimulated cultures spontaneously produced low levels of PA during myogenesis, peak activity appearing shortly after cell fusion. In cultures infected with the temperature-sensitive ts-68 mutant of RSV, PA activity was sevenfold higher at 41 C than in uninfected controls, a still greater increase in activity being evident in infected cultures at 37 C. PMA also induced PA activity in muscle cell cultures, max stimulation occurring 5 hr after exposure to 81-162 nanoM PMA. PMA also strongly inhibited the fusion of myoblasts into myotubes and altered the gross morphology of myotubes in cultures. There was no increase in DNA synthesis. Retinoic acid in the concentration range 10^{-8} to 10^{-5} M also stimulated PA synthesis in myogenic cultures. Dibutyryl cyclic (C) cAMP and cholera toxin weakly enhanced PA synthesis by myogenic cultures, but they profoundly depressed enzyme production by chick embryo fibroblasts. This suggests that enzyme induction by RSV and PMA is not mediated primarily via their effects on cAMP metabolism. (41 refs)

79-0864 Models of the Molecular Structure of Receptors for the Tumor-promoting Agents Prostaglandins and PMA (Meeting Abstract). (Eng) Smythies, J. R. (Univ. Alabama in Birmingham, Birmingham, AL, 35294); Wright, J. *Biophys J* 25(2, part 2): 159a; 1979. (no refs)

79-0865 Particle-enhanced Transport of Chemical Carcinogens Studied by Fluorescence Spectroscopy (Meeting Abstract). (Eng) Lakowicz, J. R. (Univ. Minnesota, Navarre, MN, 55392); Bevan, D. R. *Biophys J* 25(2, part 2): 262a; 1979. (no refs)

79-0866 Interaction of Aflatoxins with Human Liver In Vivo and In Vitro (Meeting Abstract). (Eng) Kirk, C. (Cancer Res. Center, Columbia, MO, 65205); Yourtee, D. *Biophys J* 25(2, part 2): 233a; 1979. (no refs)

79-0867 Effects of the Tumor-promoting Agent 12-O-Tetradecanoylphorbol-13-acetate on Normal and "Preneoplastic" Mouse Submandibular Gland Epithelial Cells In Vitro. (Eng) Knowles, M. A. (Dept. Oncology, Middlesex Hosp. Medical Sch., London W1P 7PN, England). *J Natl Cancer Inst* 62(2): 349-352; 1979.

The effect of the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) was studied in mixed primary cultures of mouse submandibular gland and in slowly proliferating preneoplastic epithelial foci derived from these cultures. The primary cultures received one of the following treatments: (1) 0.05% dimethyl sulfoxide for 24 hr on days 4-5 of culture [DMSO(a)] followed by 0.05% DMSO for 72 hr weekly [DMSO(b)]; (2) DMSO(a) followed by weekly 0.05 µg/ml TPA + DMSO(b); (3) 0.1 µg/ml 7,12-dimethylbenz(a)anthracene (DMBA) + DMSO(a) followed by DMSO(b); and (4) 0.1 µg/ml DMBA + DMSO(a) followed by 0.05 µg/ml TPA + DMSO(b). During the first 30 days, TPA-treated cultures were indistinguishable from the others. The development of three-dimensional epithelial ducts, which was seen at 30-60 days in the cultures not treated with TPA, was markedly inhibited in TPA-treated cultures. At 100 days, the incidence of slow-growing foci in cultures treated with DMBA/DMSO/TPA was 4.24/100 explants (after correction for DMBA-induced toxicity). The corresponding number of foci in the other cultures was 1.40 for DMSO/DMBA, 0.86 for DMSO/DMSO, and 0.79 for DMSO/TPA. TPA had no effect on the emergence of tumorigenic cell lines at a late stage in culture (150 days) or on the development of such lines from nine preexisting foci derived from non-TPA-treated cultures. Epithelial proliferation, as shown by the ³H-thymidine labeling index and mitotic index, seemed to increase during treatment with TPA and then to fall between the weekly treatments. The finding of both tumor promotional activity and an effect on cell differentiation for TPA suggests that the two are related. (16 refs)

79-0868 Stimulation of the Synthesis of the H1 and H3 Histone Fractions of Mouse Epidermis by 12-O-Tetradecanoylphorbol-13-acetate. (Eng) Raineri, R. (McArdle Lab. Cancer Res., Univ. Wisconsin Medical Center, Madison, WI, 53706); Simsiman, R. C.; Boutwell, R. K. *Cancer Lett* 5(5): 277-284; 1978.

In this two-part study, epidermal histones from female CD-1 mice were fractionated chemically and separated electrophoretically, and incorporation of isotopically labeled precursor into specific histone fractions was determined following treatment of mice with 12-O-tetradecanoylphorbol-13-acetate (TPA). The five fractions resulting from chemical treatment were subjected to acrylamide gel electrophoresis (EP) at pH 3.2 using 15% gels. Their migration sequence was the same as that reported for calf thymus histones. Parallel EP of unfractionated histone extract confirmed identification of the five bands as the H1, H4, H3, H2B, and H2A histone fractions. In the second study, 17 nanomoles of TPA in acetone were applied to the shaved back skin of mice 24 hr before sacrifice; they were inoculated ip with 100 µCi ³H-lysine 1 hr before sacrifice. Aliquots from the crude histone extract were subjected to cellulose acetate and acrylamide gel EP. TPA increased the incorporation of lysine into epidermal histone fivefold, and the histone extract contained five major electrophoretic bands regardless of pretreatment with TPA. Compared with histone bands from control mice, there were large increases in ³H-lysine incorporation into H1 and H3 and smaller but significant increases in incorporation into H2B, H2A, and H4. The amount of ³H-lysine incorporated was not related to the quantity of each histone, in spite of the fact that histone synthesis was previously found to be coupled to DNA synthesis in mouse skin epidermis. The relationship of histone to DNA may be altered by certain phorbol esters, a suggestion that is compatible with the concept that gene activation is the decisive function of these esters in tumor formation. (18 refs)

79-0869 Comparison of Benzo(a)pyrene Metabolism by Human Peripheral Blood Lymphocytes and Monocytes. (Eng) Vaught, J. B. (Dept. Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY, 14263); Gurtoo, H. L.; Paigen, B.; Minowada, J.; Sartori, P. *Cancer Lett* 5(5): 261-268; 1978.

An improved, sensitive, high-pressure liquid chromatography (HPLC) assay of benzo(a)pyrene (BP) metabolites was used to examine the profiles elaborated by human lymphocytes and monocytes. As little as 10 x 10⁶ cells and only 1 hr incubation with BP were required. Human lymphocytes and monocytes in culture were exposed to 10 µM benz(a)anthracene 24 hr before harvest to induce aryl hydrocarbon hydroxylase (AHH) activity. The cells from these induced cultures were then incubated with ³H-BP (0.1 µCi micromole) for 1 hr and then analyzed by HPLC. Both cell types produced primarily 3-hydroxy-BP, 9-hydroxy-BP, quinones, and dihydrodiols, particularly, 7,8-dihydrodiol. The

lymphocytes also produced a peak slightly more polar than the marker 9,10-dihydrodiol peak. Addition of 1,1,1-trichloropropene oxide (10^{-3} M) to the reaction mixture resulted in loss of the 7,8-dihydrodiol peak in both cell types. α -Naphthoflavone (10^{-3} M), an inhibitor of polycyclic aromatic hydrocarbon-inducible cytochrome, caused an overall decrease in BP metabolism. Since diol epoxides at the 7,8,9,10-positions of BP have been postulated as the ultimate carcinogen metabolites, the production of 7,8-dihydrodiol by both monocytes and lymphocytes is significant in indicating the likely potential of human tissues to activate BP. (29 refs)

79-0870 Enzymic Formation of Free Radical from Anthanthrene and 10-Azabenz[a]pyrene Lacking the Bay Region. (Eng) Kodama, M. (Biophysics Div., National Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-Ku, Tokyo 104, Japan); Kimura, T.; Nagata, C.; Shudo, K. *Gann* 69(6): 865-866; 1978.

The enzymatic formation of free radicals from aromatic hydrocarbons lacking the bay region was studied by electron spin resonance. Incubation of anthanthrene with liver microsomes from methylcholanthrene-treated rats yielded a free radical with a g-value of 2.005 and a linewidth of 9.8 gauss. The free radical was tentatively identified as the semiquinone radical. The free radical formed from 10-azabenz(a)pyrene had a g-value of 2.004 and a linewidth of 14.3 gauss; it was tentatively identified as 6-oxy-10-azabenz(a)pyrene. The two free radicals bound covalently with polyguanylic acid, retaining their free radical forms. The data indicate that the formation of a free radical is involved in the activation process of anthanthrene and 10-azabenz(a)pyrene. (7 refs)

79-0871 Methylcholanthrene Induced Murine Primitive Neuroectodermal Tumor: Ultrastructure and Nuclear RNA Polymerase Activity. (Eng) Slagel, D. E. (Lab. Neurochemistry, Div. Neurosurgery, Dept. Surgery, Univ. Kentucky Coll. Medicine, Lexington, KY, 40506). *Acta Neuropathol (Berl)* 44(3): 173-182; 1978.

Examination was made of the histology, ultrastructure, and nuclear RNA polymerase activity of a murine primitive neuroectodermal tumor derived by serial transplantation from an experimental ependymoblastoma induced by methylcholanthrene. Morphologically, the tumor consisted of cuboid cells with pleomorphic nuclei often arranged in rosettes, but the usual polarity seen in an ependymoma rosette was lacking. The nuclei contained 1-10 large nucleoli. Ultrastructurally, the cells forming the rosette pattern lacked the apical and basal regions found in ependymoma cells. Desmosomes and zonula occludens were not observed. The most prominent ultrastructural feature was irregularly lobulated nuclei. A-type virus particles were seen in the cytoplasm, and B-type virus particles were seen budding into the extracellular space. The nuclear RNA synthesizing activity was very high

(guanosine triphosphate incorporation, 0.22 nanomole/mg DNA/hr). α -Amanitin and adriamycin inhibited RNA synthesis in the tumor nuclei by 42% and 58%, respectively. The ultrastructure of the tumor suggests that a large part of nuclear RNA synthesis may be carried out by RNA polymerase I in the nucleoli of the tumor cells. (73 refs)

79-0872 Metabolic Activation of 3-Methylcholanthrene: Mutagenic and Transforming Activities of the 9,10-Dihydrodiol. (Eng) Malaveille, C. (International Agency Res. Cancer, 150 cours Albert Thomas, 69372 Lyon, France); Bartsch, H.; Marquardt, H.; Baker, S.; Tierney, B.; Hewer, A.; Grover, P. L.; Sims, P. *Biochem Biophys Res Commun* 85(4): 1568-1574; 1978.

3-Methylcholanthrene (3-MC) and five related dihydrodiols were tested for microsome-mediated mutagenicity toward *Salmonella typhimurium* TA100, for the induction of mutation to 8-azaguanine resistance in V79 Chinese hamster cells, and for malignant transformation in M2 mouse fibroblasts. In both mutagenicity test systems, trans-9,10-dihydro-9,10-dihydroxy-3-methylcholanthrene was considerably more active than 3-MC and cis-2 α ,3-dihydroxy-, trans-4,5-dihydro-4,5-dihydroxy-, trans-7,8-dihydro-7,8-dihydroxy-, and trans-11,12-dihydro-11,12-dihydroxy-3-MC. At 1 μ g/ml medium, the 9,10-diol induced the formation of more transformed malignant foci in cultures of M2 cells than 3-MC, but at higher and lower concentrations this difference was not apparent. The other diols were either inactive or only weakly active in this test system. Cells transformed by the 9,10-dihydrodiol yielded tumors on injection into C3H/HeJ mice. These results are consistent with the hypothesis that the metabolic activation of 3-MC involves metabolism in the 7,8,9,10-ring and that this activation proceeds through formation of the 9,10-diol and its subsequent conversion into the related vicinal diol-epoxide, 9,10-dihydro-9,10-dihydroxy-3-methylcholanthrene 7,8-oxide, a bay region diol-epoxide. (16 refs)

79-0873 Changes in Cell Population Kinetics During Epidermal Carcinogenesis. (Eng) Fukuda, M. (Dept. Pathology, Kyoto Prefectural Univ. Medicine, Kawaramachi, Hirokoji, Kami-Kyoku, Kyoto, Japan); Okamura, K.; Rohrbach, R.; Bohm, N.; Fujita, S. *Cell Tissue Kinet* 11(6): 611-621; 1978.

Changes in cell population kinetics in response to wounding were compared in the hyperplastic epidermis (HE), papillomas, squamous cell carcinomas, and normal tissue of male dd mice. The HE and the tumors were induced by topical applications of 20-methylcholanthrene (0.5% soln) on shaved dorsal epidermis 2x/wk for up to 20 wk. In wounding experiments, a linear incision was made by a razor blade down to underlying muscle layers. Flash (in wounding experiments) or continuous DNA labeling with tritiated thymidine was

used for cell-cycle analyses. G_0 cells were absent in the HE, papillomas, and carcinomas. In HE, the proliferating cells (PC's) were localized in the basal layer. The PC zone was enlarged in the papillomas compared with that in normal or HE, but it was still localized in several layers above the basement membranes. PC's were distributed throughout most of the carcinoma tissue. The continuous labeling curves for HE and the tumors increased almost linearly and reached 100%, indicating the absence of heterogeneous cell subpopulations. Normal responses to wounding were preserved in the HE; ie, shortening of cell-cycle time and reversible enlargement of the PC zone were still observed, in spite of the absence of G_0 cells. These responses were not seen in the tumors; ie, flexible mechanisms controlling irreversible cell differentiation to mature cells and the duration of the cell cycle were lacking. In both tumors, the irreversible differentiation to mature cells also seemed fixed at a quantitatively low level in the PC's, because the PC zone was enlarged irreversibly, without showing any response to wounding. With the fixed probability of cell differentiation at a decreased level, the PC population in the tumor tissues will continue to grow larger and larger, in spite of the fixed prolongation of the cell cycle. (27 refs)

79-0874 Two-stage Malignant Transformation in Hamster Embryo Cells. (Eng) Poiley, J. A. (Chemical Carcinogenesis Program, NCI, Frederick Cancer Res. Center, Frederick, MD, 21501); Raineri, R.; Pienta, R. J. *Br J Cancer* 39(1): 8-14; 1979.

The ability of 3-methylcholanthrene (MCA), 12-O-tetradecanoylphorbol-13-acetate (TPA), and/or dibenz(a,h)anthracene (DBA) to induce transformation in primary hamster embryo cells was studied. In cells treated with MCA or MCA + TPA, morphological transformation occurred at the same time regardless of treatment. Cells treated with MCA alone produced rapidly growing colonies in soft agar and induced more tumors in hamsters with a slightly shorter latent period, compared with cells treated with MCA + TPA. When TPA was administered simultaneously with or 7 days after MCA, transformation, growth in soft agar, and the ability to induce tumors were inhibited. Treatment with TPA 27 days after MCA reduced the latent period to morphological transformation and increased the ability of the cells to induce tumors. A promoting effect was found when cells treated with a subtransforming dose of DBA followed 7 to 30 days later by TPA. The data indicate that TPA acts as an inhibitor or promoter, depending on the length of time between carcinogen treatment and TPA administration. (12 refs)

79-0875 Changes in the Synthesis of Normal Antibodies to One of the Common Enterobacterial Antigens During the Carcinogenesis in Rats and Oncogenesis in Humans. (Rus) Montsevichiute-Eringene, E. V. (Res. Inst. Oncology, Vilnius, USSR). *Vestn Akad Med Nauk SSSR* (12): 69-71; 1978.

The normal level of antibodies to the common enterobacterial antigen (CEBA) was used for evaluation of the immunological status of Wistar rats with induced tumors and of people with subgastritis and achlorhydria and cancer. The rats were inoculated sc with 3-methylcholanthrene (MC: 5 mg) or with benzo(a)pyrene (BP: 1 mg) in peach kernel oil. Administration of the carcinogens resulted in a period of primary stimulation of antibody synthesis (62% of the sera from 4- to 5-mo-old treated rats contained antibodies, compared with 14% of the sera from nontreated rats), followed by a period of immunodepression (66% of the sera did not contain normal antibodies) and a period of secondary immunostimulation (during the last 5 wk of the experiment, when all rats developed tumors, 76% of the sera contained antibodies). At prophylactic examinations of patients, normal antibodies to CEBA could be detected in 33% of the individuals, compared with 46% of the patients with achlorhydria and 72.1% of the patients with cancer. (3 refs)

79-0876 Chemical Carcinogenesis in Nude Mice: Comparison Between Nude Mice from Homozygous Matings and Heterozygous Matings and Effect of Age and Carcinogen Dose. (Eng) Stutman, O. (Cellular Immunobiology Section, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021). *J Natl Cancer Inst* 62(2): 353-358; 1979.

The incidence and latency periods for local tumor development after injection of 3-methylcholanthrene (3-MC: 0.10, 0.01, 0.02, 0.05, or 0.10 mg sc) were compared in 30-day-old nude mice (nu/nu partially inbred on the CBA/H background) derived from homozygous (nu/nu x nu/nu) or heterozygous matings (nu/+ x nu/+). At these doses, neither tumor incidence nor latency period differed between the two groups of nude mice or between these mice and immunologically normal controls. This result was also observed when wt-adjusted doses of 3-MC equivalent to 0.02 or 0.10 mg in the 30-day-old mice were given at 120, 210, or 360 days of age. However, an age effect was observed, since tumor incidence decreased in nude and normal mice when 3-MC was administered at 210 and 360 days of age, especially in mice inoculated with the lower dose of 3-MC. 3-MC doses of 0.01-0.05 mg had no detectable immunosuppressive effects on normal mice. These findings indicate that the lack of differences in tumor incidence or latency periods between nude and normal mice following 3-MC administration cannot be ascribed to putative thymus function in nude mice bred from heterozygous parents, carcinogen dose, immunodepressive effects of the carcinogen, or age of the animals at the time of carcinogen administration. The results corroborate previous findings that nude mice do not show an increased risk for tumor development after exposure to 3-MC. (53 refs)

79-0877 Synthesis of the Dihydrodiols and Diol Epoxides of Benzo(e)pyrene and Triphenylene. (Eng) Harvey, R. G. (Ben May Lab. Cancer Res., Univ. Chicago,

Chicago, IL, 60637); Lee, H. M.; Shyamasundar, N. *J Org Chem* 44(1): 78-83; 1979.

Synthesis of the "bay region" dihydrodiols of benzo(e)pyrene and triphenylene and the corresponding anti-isomeric diol epoxides is described. Nuclear magnetic resonance analysis indicated that all four chemicals exist preferentially in the diaxial conformation. Both diol epoxides, derived from hydrocarbons inactive as carcinogens, were inactive as inhibitors of the ϕ X 174 DNA virus, whereas the analogous *anti*-diol epoxide of benzo[a]pyrene was highly potent. (35 refs)

79-0878 Molecular Calculations with the Nonempirical ab initio MODPOT, VRDDO, and MODPOT/VRDDO Procedures. IX. Carcinogenic Benzo(a)pyrene and its Metabolites Using a MERGE Technique. (Eng) Kaufman, J. J. (Dept. Anesthesiology, John Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205); Popkie, H. E.; Palalikit, S.; Hariharan, P. C. *Int J Quantum Chem* 14(6): 793-800; 1978.

Quantum chemical calculations were carried out on benzo(a)pyrene (BP) and its dihydrodiol and dihydrodiol epoxide metabolites. Computations were carried out using two programs: ab initio effective core model potentials (MODPOT) and variable retention of diatomic differential overlap (VRDDO). A new MERGE technique allowing reuse of integrals of a common skeletal fragment was also utilized. Preliminary calculations indicated the β,β,β conformation of BP-7,8-dihydrodiol-9,10-epoxide to be the most stable of the geometries tested. The data also confirmed the hypothesis that the epoxide ring opening in this compound would favor the O remaining on C₉ rather than C₁₀. The total energy corresponding to opening the ring to a 90 degree angle O-C₉-C₁₀ is lower than for opening the ring to a 90 degree angle O-C₉-C₈. The lowest energy surface for opening the epoxide ring to a 90 degree C₁₀-C₉-O angle leads to a slightly more negative change on the C₁₀ (-0.20) than when the epoxide ring is completely closed (-0.12). As the ring is opened past a 90 degree O-C₉-C₁₀ or O-C₁₀-C₉ angle, there is some indication that there may be a mixing of configurations. (13 refs)

79-0879 Effects of Benzo(a)pyrene Adducts on DNA Synthesis In Vitro. (Eng) Yamaura, I. (Sloan-Kettering Inst. Cancer Res., Walker Lab., 145 Boston Post Road, Rye, NY, 10580); Marquardt, H.; Cavalieri, L. F. *Chem Biol Interact* 23(3): 399-407; 1978.

The diol epoxide derivatives of the polycyclic aromatic hydrocarbon benzo(a)pyrene (BP), (\pm)-7 β ,8 α -dihydroxy-9 β ,10 β -epoxy-7,8,9,10-tetrahydro BP, and (\pm)-7 β ,8 α -dihydroxy-9 α ,10 α -epoxy-7,8,9,10-tetrahydro BP (*cis* and *trans* isomers, respectively), have been used to make adducts in the homopolymers polyribocytidylic acid, polydeoxycytidylic acid, polyriboadenylic acid, and polydeoxyadenylic acid. In

conjunction with appropriate oligomers as primers, these polynucleotides were used as templates for DNA synthesis with avian myeloblastosis virus DNA polymerase or *Escherichia coli* Pol I DNA polymerase. Results revealed that the size of the DNA product is not significantly decreased by the presence of these adducts in the template. Furthermore, the presence of these adducts does not lead to increased incorporation of erroneous bases. This evidence, coupled with kinetic data, suggests that these polymerases can bypass a site containing an adduct on the template without leaving a gap or causing misincorporation of a base. It is concluded that mutagenesis by BP may not be attributable to either of these mechanisms. (28 refs)

79-0880 Comparison of In Vivo and In Vitro Binding of Polycyclic Hydrocarbons to DNA. (Eng) Eastman, A. (Dept. Biochemistry, Univ. Vermont Coll. Medicine, Burlington, VT, 05405); Sweetenham, J.; Bresnick, E. *Chem Biol Interact* 23(3): 345-353; 1978.

The in vivo binding of ³H-benzo(a)pyrene (BP) and ³H3-methylcholanthrene (3MC) to liver and lung DNA was studied in A/J mice. Only in liver was there any reduction in total DNA-bound radioactivity between 4 and 24 hr after hydrocarbon administration. DNA was fractionated on Sephadex LH-20 after enzymatic digestion. A single deoxyribonucleoside-BP adduct was detected, but two major 3MC-adducts were observed. With both BP and 3MC, three additional peaks of radioactivity eluted rapidly in the lung DNA experiments and a fourth was noted with liver DNA. The nucleoside-bound adducts from lung represented a much larger proportion of the total radioactivity than did those from liver. In vitro analysis of 3MC binding to DNA showed that the nucleoside-bound adducts were predominantly deoxyguanosine-dependent; however, the early peaks were independent of base, suggesting binding to another part of the DNA molecule, perhaps phosphate, ie, phosphotriesters. The higher proportion of aryl alkylated nucleosides in the lung may be related to the susceptibility of this organ to polycyclic hydrocarbon-induced carcinogenesis. (32 refs)

79-0881 Effects of Microsomal Enzyme Inducers In Vivo and Inhibitors In Vitro on the Covalent Binding of Benzo(a)pyrene Metabolites to DNA Catalyzed by Liver Microsomes from Genetically Responsive and Nonresponsive Mice. (Eng) Boobis, A. R. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20014); Nebert, D. W.; Pelkonen, O. *Biochem Pharmacol* 28(1): 111-121; 1979.

Increases or decreases in nine benzo(a)pyrene (BP) metabolite-nucleoside peaks caused by the use of various microsomal enzyme inducers in vivo and inhibitors in vitro were examined with respect to genetically responsive or nonresponsive mice, in an attempt to understand and identify changes in

reactive BP intermediates that bind to DNA. The peaks were named A (most polar) through I (least polar). 3-Methylcholanthrene (3-MC), 2,3,7,8-tetrachlorodibenzo-p-dioxin, phenobarbital, Aroclor 1254, pregnenolone-16 α -carbonitrile, or ethanol was administered in vivo to responsive C57BL/6N or nonresponsive DBA/2N mice. The rises or falls in the peaks were noted when liver microsomes from control or 3-MC-treated C57BL/6N or DBA/2N mice were incubated with ³H-BP and microsomal enzyme inhibitors. All interpretations concerning the binding of metabolites to DNA were consistent with non-K-region oxygenation of BP being mediated predominantly by cytochrome(s) P₁-450 and K-region oxygenation of BP being catalyzed predominantly by form(s) of P-450 other than P₁-450. All biological perturbations were consistent with the following assignments. The major reactive intermediate of BP contributing to each peak was suggested to be: peaks A and C, an unknown dihydrodiol oxide; peaks B, D, F, and I, quinones oxygenated further (or quinone-derived free radicals); peak E, both cis- and trans-7,8-diol-9,10-epoxides; peak F', the 7,8-oxide; peak G, the 4,5-oxide; and peak H, an unknown phenol oxide. The major metabolite(s) contributing to all peaks except F' and G involve(s) more than a single monooxygenation by forms of cytochrome P-450. All peaks except G appear to be predominantly associated with BP metabolism mediated by P₁-450 and, therefore, controlled by the *Ah* locus. The use of these microsomal inducers or inhibitors--combined with the underlying genetic predisposition of the individual, tissue, or cell culture system under study--demonstrates that the balance between P-450 and epoxide hydase and the ratio of each form of P-450 to the other forms of P-450 can influence markedly the quantity and quality of reactive intermediates of BP that bind to DNA. (43 refs)

79-0882 Fluorescence Study of DNA-Complexes Formed after Metabolic Activation of Benzo(a)-pyrene Derivatives. (Eng) Dock, L. (Dept. Forensic Medicine, Karolinska Institutet, S-104 01 Stockholm 60, Sweden); Undeman, O.; Graslund, A.; Jernstrom, B. *Biochem Biophys Res Commun* 85(4): 1275-1282; 1978.

Several benzo(a)pyrene (BP) phenols and dihydrodiols were incubated with liver microsomes obtained from 3-methylcholanthrene-treated rats and calf thymus DNA for 30 min. The modified DNA, native or denatured, was assayed by fluorescence for bound metabolites. Of the derivatives tested, only 2-hydroxybenzo(a)-pyrene (2-OH-BP), 9-hydroxybenzo(a)-pyrene (9-OH-BP), and trans-7,8-dihydro-7,8-dihydroxybenzo(a)pyrene (BP 7,8-dihydrodiol) yielded detectable amounts of DNA-bound products. 1-Hydroxy-, 3-hydroxy-, 7-hydroxy-, trans-9,10-dihydro-9,10-dihydroxy-, and trans-4,5-dihydro-4,5-dihydroxy-BP did not give detectable DNA-bound products. In contrast to the product(s) from 9-OH-BP, the metabolites of 2-OH-BP and BP 7,8-dihydrodiol, both strong carcinogens, had similar excitation spectra. The fluorescence intensity associated with products of BP 7,8-dihydrodiol and 2-OH-BP was enhanced severalfold

after denaturation of DNA, but denaturation of DNA modified by products from 9-OH-BP resulted in a 50% reduction of the fluorescence intensity. These data indicate that there are structural similarities in the DNA complexes formed after metabolic activation of 2-OH-BP and BP 7,8-dihydrodiol. The results with 9-OH-BP also indicate that DNA binding alone is not sufficient for carcinogenicity. Factors such as the structures of the DNA-binding intermediate and the subsequent DNA complex must also be considered. (23 refs)

79-0883 Mutagenic Substances as Possible Senility Factors. (Eng) Sirtori, C. (Multiscreening Lab., Gaslini Inst., Genoa, Italy); Paganuzzi, M.; Lombardo, C.; Scalese, S.; Ruzzon, T. *Pharmacol Res Commun* 10(9): 809-912; 1978.

The results of several varied studies are reported briefly. The urine of 11/12 smokers was positive in the Ames Salmonella mutagenicity assay; that of 12/12 nonsmokers was negative. Thin-layer chromatography showed that benzo(a)pyrene (BP) is present in higher amounts in the urine of nonsmokers, but probable BP metabolites are present only in the urine of smokers. Routine use of contraceptive ovuli (not pills) containing anti-inflammatory substances may have anti-cervical cancer properties and antimutagenic properties in spermatocytes. Mutagenic or carcinogenic agents are also factors that favor senility. (9 refs)

79-0884 Induction, Modification and Inhibition of Rat Liver Microsomal Benzo(a)pyrene Hydroxylase; Correlation with the S-9-Mediated Mutagenicity of Benzo(a)pyrene. (Eng) Razzouk, C. (Lab. Biotoxicology, Univ. Louvain, Sch. Pharmacy, U.C.L.-73.69, B-1200 Brussels, Belgium); Agazzi-Leonard, E.; Cumps, J.; Poncelet, F.; Mercier, M.; Roberfroid, M. *Biochem Biophys Res Commun* 85(3): 1007-1016; 1978.

The effects of various pretreatments in vivo and of various inhibitors in vitro on the activity of rat liver microsomal benzo(a)pyrene hydroxylase were analyzed and correlated with the liver microsome (S-9)-mediated mutagenicity of benzo(a)-pyrene (BP) to *Salmonella typhimurium* strain TA1538. Adult male Wistar rats were treated with phenobarbital (PB), 3-methylcholanthrene, (3-MC), 2-fluorenylacetylamide (2FAA), or 4-fluorenylacetylamide (4AAF) before preparation of the liver microsomal fraction. At a low concentration of both proteins (4.3 μ g/ml) and BP (0.05-2 μ M), the V_{max} and K_m of the BP hydroxylase from 3-MC-treated rats were 2.4 times higher and 10 times lower than the same parameters of control enzymatic preparations, indicating that 3-MC induced (V_{max}) and modified (K_m) the enzyme activity. 3-MC pretreatment also increased the enzyme-mediated mutagenicity. Pretreatment with PB or 2FAA did not induce or modify BP hydroxylase and did not increase the S-9-mediated mutagenicity of BP. Of the various inhibitors

tested, only Miconazole inhibited all the tested microsomal preparations and reduced S-9-mediated mutagenicity. The inhibitory effects of 7,8-benzoflavone and SKF525A were limited to enzyme preparations from 3-MC-induced and control or PB-induced rats, respectively. Thus, rat liver microsomal BP hydroxylase induction and modification correlate with the S-9-mediated mutagenicity of BP. (22 refs)

- 79-0885 Base Specificity in the Binding of Benzo(a)pyrene Diol Epoxide to Simian Virus 40 DNA.** (Eng) Mengle, L. (Lab. Chemical Biodynamics, Lawrence Berkeley Lab., Univ. California, Berkeley, CA, 94720); Gamper, H.; Bartholomew, J. *Cancer Lett* 5(3): 131-137; 1978.

The simian virus 40 (SV40) DNA molecule, isolated from SV40-infected TC-7 African green monkey kidney cells, was used to assess the effect of the structure of DNA on its binding to 7 β ,8 α -dihydroxy-9 α ,10 α -epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (BP diol epoxide). ¹⁴C-SV40 DNA (2.5 μ g) and ³H-BP-diol epoxide (0.013-0.13 μ g) were incubated for 24 hr, and the modified DNA was digested to completion with 10 units of Hind III restriction endonuclease. The six characteristic fragments that resulted were separated by polyacrylamide gel electrophoresis. Binding of BP diol epoxide was proportional to the molar ratio of hydrocarbon to DNA in the reaction mixture. In subsequent experiments, SV40 DNA was reacted with the diol epoxide at a molar ratio of 7.0×10^{-3} , thereby inducing 0.60 adduct/molecule of DNA. This level of adduct formation was approx that seen in vivo and it had no effect on Hind III digestion. The extent of adduct formation was not strictly dependent on DNA length, and this appears to reflect variability in the guanine-cytosine (G-C) content of the fragments. Hydrocarbon binding to the fragments was proportional to their G-C content, reflecting selective reaction of the hydrocarbon with deoxyguanosine residues. Despite the low level of modification, no sites unusually susceptible to alkylation were detected. (18 refs)

- 79-0886 Comparison of the In Vitro Mutagenicity and Metabolism of Dimethylnitrosamine and Benzo(a)pyrene in Tissues from Inbred Mice Treated with Phenobarbital, 3-Methylcholanthrene or Polychlorinated Biphenyls.** (Eng) Hutton, J. J. (Medical Services, VA Hosp., Lexington, KY, 40507); Meier, J.; Hackney, C. *Mutat Res* 66(1): 75-94; 1979.

Homogenates of liver, lung, kidney, stomach, small intestine, and colon from eight mouse strains were compared for their ability to metabolize benzo(a)pyrene (BP) and dimethylnitrosamine (DMN) to mutagens. CF1, AKR/J, AU/SsJ, DBA/2J, SWR/J, A/J, C3H/HeJ, and C57BL/6J females were untreated or inoculated ip with phenobarbital (PB), 3-methylcholanthrene (MC), or Aroclor 1254 (AR) prior to

sacrifice. Mutagenesis was detected using *Salmonella typhimurium* TA92 and TA98. AR and MC were good inducers of aryl hydrocarbon hydroxylase (AHH) activity in liver from aromatic hydrocarbon-responsive strains, but not in liver from nonresponsive strains. Metabolism of BP to mutagens by liver homogenates was correlated with extent of AHH induction. Basal activities of AHH and dimethylnitrosamine demethylase (DMND) were correlated in liver and lung from untreated mice. DMND activities were increased less than twofold by PB, MC, or AR. Livers from untreated mice converted DMN and BP to mutagens, but there was no significant quantitative correlation between DMND activity and DMN mutagenesis or between AHH activity and BP mutagenesis. Conversion of DMN and BP to mutagenic metabolites could not be detected in homogenates from kidney, stomach, small intestine, or colon. These studies indicate that mouse strain, organ, and test substance are important variables in assessing the potential effect of microsomal enzyme-inducing agents on the metabolism of mutagens. (45 refs)

- 79-0887 Mutagenicity and Cytotoxicity of Light-activated Procarcinogens (Meeting Abstract).** (Eng) Barnhart, B. J. (Los Alamos Scientific Lab., Univ. of California, Los Alamos, NM, 87545); Cox, S. H.; Okinaka, R. T. *J Cell Biol* 79(2, part 2): 388a; 1978. (no refs)

- 79-0888 Effect of Chronic Ethanol Ingestion on Intestinal Metabolism and Mutagenicity of Benzo(a)pyrene.** (Eng) Seitz, H. K. (Alcoholism Res. and Treatment Center, Bronx V.A. Hosp., New York, NY); Garro, A. J.; Lieber, C. S. *Biochem Biophys Res Commun* 85(3): 1061-1066; 1978.

The effect of chronic ethanol ingestion on intestinal microsomal cytochrome P-450 level, benzo(a)pyrene hydroxylase activity, and activation of benzo(a)pyrene (BP) to a mutagen was studied in male Sprague-Dawley rats. The rats were fed a diet containing 36% of total calories either as ethanol or as isocaloric carbohydrates for 3-4 wk before sacrifice. There was a threefold increase in intestinal microsomal cytochrome P-450 level in the ethanol-fed rats compared with that in the controls [26.0 vs 8.9 picomoles (pmol)/mg microsomal protein]. Intestinal BP hydroxylase activity was also increased threefold in the ethanol-fed rats (18.1 vs 6.6 pmol 3-hydroxy-BP/mg microsomal protein/min). When BP was tested for mutagenic activity to *Salmonella typhimurium* strain TA100 in the presence of microsomes from ethanol-fed and control animals, clear dose-response curves were observed. Over the entire range of BP concentrations studied, the levels of revertants were highest with microsomes of ethanol-fed animals. The results suggest that the increased incidence of cancer among alcoholics may be due to the enhanced capacity of these individuals to activate procarcinogens in the intestine. (25 refs)

79-0889 Benzo(a)pyrene-initiated Leukemia in Mice: Association with Allelic Differences at the *Ah* Locus. (Eng) Nebert, D. W. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20014); Jensen, N. M. *Biochem Pharmacol* 27(1): 149-151; 1979.

The induction of leukemia by benzo(a)pyrene (BP) was studied in mice responsive (*Ah^b*) and nonresponsive (*Ah^d*) to the induction of cytochrome P₁-450 and P-448 and monooxygenase activities by polycyclic aromatic hydrocarbons. Groups of 30 nonresponsive *Ah^d/Ah^d* or responsive *Ah^b/Ah^d* mice were given 12 or 6 mg BP/kg/day po. At 12 mg/kg/day, all *Ah^d/Ah^d* mice died before 110 days on the diet; none of the 30 *Ah^b/Ah^d* had died by day 100; 3 died after 150 days. At 6 mg/kg/day, 24/30 *Ah^d/Ah^d* mice and 2/20 *Ah^b/Ah^d* mice had died after 240 days on the diet. Mice that became ill and died did not have the expected hypoplastic or aplastic bone marrow but rather developed hematopoietic neoplasms, especially of the lymph nodes, spleen, and thymus. When α -naphthoflavone (ANF) was added to the diet at a dose 20 times greater than that of BP (6 mg/kg/day), the incidence of leukemia was prevented almost completely and the general health of the *Ah^d/Ah^d* mice remained as good as that of the *Ah^b/Ah^d* mice receiving 12 mg BP/kg/day. These data suggest that the ANF-sensitive metabolism of BP, presumably mediated by cytochrome P₁-450 in the bone marrow of *Ah^d/Ah^d* mice, is responsible for the reticuloendothelial malignancies. These results may be explained on the basis of "first-pass elimination" kinetics. (13 refs)

79-0890 UDP-Glucuronosyl Transferase and the Conjugation of Benzo(a)pyrene Metabolites to DNA. (Eng) Fahl, W. E. (Dept. Pharmacology, Univ. Wisconsin Medical Sch., Madison, WI, 53706); Shen, A. L.; Jefcoate, C. R. *Biochem Biophys Res Commun* 85(3): 891-899; 1978.

The role of uridine diphosphate (UDP)-glucuronosyl transferase in the conjugation of benzo(a)pyrene (BP) metabolites to DNA was studied. Following the addition of UDP-glucuronic acid (UDPGA) to incubations containing ³H-BP and liver microsomes from methylcholanthrene-induced rats, there were large decreases in the levels of BP quinones and 3-phenol, which were half max at 1.0 and 1.6 mM UDPGA, respectively. The 9-phenol was less sensitive to UDPGA. Total BP metabolism increased maximally (by 38%) at 2 mM UDPGA. Treatment of the water-soluble incubation products with β -glucuronidase followed by organic extraction and high-pressure liquid chromatographic analysis of the extract and quantification of the released compounds indicated that the mixed function oxidation of BP is stimulated unselectively in the presence of 2 mM UDPGA. In the presence of calf thymus DNA, UDPGA caused a 2.7-fold increase in the conjugation of benzo(a)pyrene 7,8-dihydrodiol 9,10-oxide to DNA. Max DNA modification by the diol-oxides occurred at a UDPGA concentration (2 mM) that gave the highest level of free BP 7,8-dihydrodiol. The UDPGA-induced in-

crease in BP oxidation and concomitant increase in diol-oxide modification of DNA is consistent with the removal of product inhibition by glucuronide conjugation of an inhibitory BP metabolite. It seems, therefore, that although UDPGA and glucuronosyl transferase decrease the modification of DNA, which has been attributed to phenol-oxides, this enzyme activity may increase the carcinogenicity of BP by relieving product inhibition of cytochrome P-450. (20 refs)

79-0891 Application of CNDO/2 Theoretical Calculations to Interpretation of the Chemical Reactivity and Biological Activity of the *Syn* and *Anti* Diol Epoxides of Benzo(a)pyrene. (Eng) Yeh, C. Y. (Dept. Chemistry, Soochow Univ., Shihlin, Taipei, Taiwan, Republic China); Fu, P. P.; Beland, F. A.; Harvey, R. G. *Bioorg Chem* 7(4): 497-506; 1978.

CNDO/2 molecular orbital theoretical calculations were performed on the anti and syn diol epoxides (DE's) of benzo(a)pyrene (BP), and the results are discussed in terms of their reactivities, mutagenicities, and DNA binding. The results of the computer analysis predicted that C₁₀ would be the preferred site of nucleophilic attack on the epoxide ring, which agrees with experimental findings. Reactions with weak nucleophiles, such as methanol or water, support an S_N1 mechanism involving proton-assisted ring-opening prior to nucleophilic attack at C₁₀. With stronger nucleophiles, ring-opening is trans-stereospecific, and an S_N2 mechanism is implicated. Both isomeric BP DE's have been shown to be highly efficient alkylating agents of DNA, RNA, and purine and pyrimidine homopolymers. The structures of the major bound products following degradation to the nucleotide or nucleoside level involve covalent bonding between the C₁₀ benzylic positions of the BP DE's and the 2-NH₂ group of guanosine. Ring-opening is predominantly trans-stereospecific. These results are consistent with an S_N2 mechanism involving attack by the nucleophilic center on C₁₀ at neutral pH. The theoretical treatment did not consider the fact that the DE's formed metabolically are optically active, as are the nucleic acids and protein reactants that may contribute significantly to reactions between the two. There is some evidence that the enantiomers of the anti and syn BP DE's exhibit differences in mutagenicity; these differences are not predicted from the CNDO/2 calculations. (35 refs)

79-0892 Sustained-Release Endobronchial Carcinogenic Implants. (Eng) Shors, E. C. (Dept. Surgery, UCLA Sch. Medicine, Harbor General Hosp., Campus, Torrance, CA); Fu, P. C.; Matsumura, K.; Cohen, A. H.; Benfield, J. R. *Surg Forum* 29: 205-207; 1978.

A new method for the sustained release of benzo(a)pyrene (BP) at precise endobronchial sites in dogs and hamsters was developed. Silicone rubber implants containing 484-934 μ g BP (hamsters) or 2.93-20.53 mg (dogs) were inserted endo-

bronchially and then removed at intervals during the next 200 days. In both species, BP was released according to a one-compartment exponential function, and the release half-time was 44.4 days. The exponential release rate was 1.56%/day. Preneoplastic changes resulted in the dogs, cancers in the hamsters. (2 refs)

- 79-0893 The Petroleum-inducible Mixed-Function Oxidase of Cunner (*Tautoglabrus adspersus* Walbaum 1792): Some Characteristics Relevant to Hydrocarbon Monitoring.** (Eng) Walton, D. G. (Dept. Zoology, Univ. British Columbia, Vancouver, B.C. V6T 1W5, Canada); Penrose, W. R.; Green, J. M. *J Fish Res Board Can* 35(12): 1547-1552; 1978.

The aryl hydrocarbon hydroxylase (AHH) system of the cunner (*Tautoglabrus adspersus*) was studied to confirm the suitability of this species as a monitoring tool for environmental hydrocarbons. The hepatic benzo(a)pyrene (BP) hydroxylase and 2,5-diphenyloxazole (PPO) hydroxylase activities were twofold greater in males than in prespawning females, but the difference disappeared after spawning. Specific hydroxylase activity and the liver-somatic index decreased about 40% after starvation. Neither uninduced nor induced specific activity correlated with body or liver wt. Exposure to crude oil (0.2-2 mg/liter added to the ambient water) resulted in rapid induction of BP hydroxylation that persisted for 1 wk following exposure. Hydroxylase induction also followed force feeding of 0.1 ml crude oil or feeding of oiled mussel tissue. PPO was a safe substitute for BP in the assay. (20 refs)

- 79-0894 Analysis of Polycyclic Aromatic Hydrocarbons in Raw and Broiled Fishes.** (Jpn) Yamazaki, H. (Faculty Pharmaceutical Sciences, Osaka Univ., 133-1, Yamadakami, Suita-shi, Japan); Minami, J.; Ichikawa, T.; Kondo, M. *J Food Hyg Soc Jpn* 18(4): 368-374; 1977.

Raw, dried, and broiled (over a gas flame, unwrapped or wrapped in aluminum foil) fish were analyzed for the presence of several polycyclic aromatic hydrocarbons (PAH): benzo(a)pyrene (BP), benz(a)anthracene (BA), 1,2,5,6-dibenzanthracene (DBA), and chrysene (CS). None of these PAH were detected in the 17 samples of raw fish analyzed, which included mackerel, sardines, scabbard fish, pomfret, eel, and mackerel pike. However, BP, BA, and CS were detected in salted, dried sardines. In the 33 samples of fish broiled directly over a gas flame, the highest level of BP, BA, and CS found was 0.75, 0.39, and 0.98 $\mu\text{g}/100\text{ g}$. The av level of BP in these samples was 0.13 $\mu\text{g}/100\text{ g}$. None of these samples contained DBA. Only CS was detected in the fish that were wrapped in aluminum foil before being broiled. Only CS was detected in the gas used for broiling. The cholesterol, neutral fats, fatty acids, and carotenoids found in raw fish are assumed to be the source of the PAH detected in the broiled fish. (17 refs)

- 79-0895 Development of Induced Tumors in Rats of Different Ages.** (Bul) Maiski, I. N. (Res. Lab. Experimental Immunobiology, Moscow, USSR); Botev, B.; Airapetian, G. P.; Pokrovska, T. A.; Vatsseva, T.; Markholev, L.; Vatev, I.; Mladenov, I. *Onkologiya* 15(2): 83-87; 1978.

The effect of age on the development of chemically induced tumors was studied in Wistar rats. Animals aged 1, 3, 5, or 9 mo or > 1 yr were inoculated with benzo(a)pyrene (1.8-3.0 mg, sc). Tumor incidence increased with the age of the rats, and it was 62%, 63%, 73%, 86%, and 87%, respectively, for the five age groups. The av latent period of tumor development was 131.5, 136.7, 128.2, 133.63, and 113.8 days, respectively. (7 refs)

- 79-0896 Comparative Tumor Initiating Activity of 10-Methylbenzo(a)pyrene, 7,10-Dimethylbenzo(a)pyrene and Benzo(a)pyrene.** (Eng) Hecht, S. S. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595); Hirota, N.; Hoffman, D. *Cancer Lett* 5(3): 179-183; 1978.

The tumor-initiating activities of benzo(a)pyrene (BP), 7,10-dimethyl-BP, and 10-methyl-BP on the skin of Ha (ICR) female outbred Swiss albino mice were compared, to determine the effect of methyl substitution in the angular ring of BP. The compounds (5 or 10 μg) were applied to shaved back skin every other day for 10 doses to a total initiation dose of 50 or 100 μg . Promotion was started 10 days after completion of initiation, and it consisted of topical applications of 12-O-tetradecanoylphorbol-13-acetate (2.5 μg 3x/wk for 20 wk). BP produced 25% and 40% tumor-bearing animals at total doses of 50 and 100 μg , respectively, but no tumors were observed in either of the groups initiated with 7,10-dimethyl-BP. 10-Methyl-BP was slightly but not significantly less active than BP at the higher dose and was as active at the lower dose, producing 20% and 20% tumor-bearing animals, respectively. However, in both cases, the latent periods with 10-methyl-BP were longer than those with BP. The skin tumors were predominantly keratoacanthomas; some papillomas were also seen. These results indicate that methyl substitution at positions 7 and 10 of BP (but not at position 10 alone) was sufficient to inhibit metabolic activation via an angular ring epoxide or diol-epoxide and that alternative pathways are not effective for activation in mouse skin. (20 refs)

- 79-0897 Tumorigenicity of Benzo(a)pyrene 4,5-, 7,8-, 9,10-, and 11,12-Oxides in Newborn Mice.** (Eng) Wislocki, P. G. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105); Kapitulnik, J.; Levin, W.; Conney, A. H.; Yagi, H.; Jerina, D. M. *Cancer Lett* 5(4): 191-197; 1978.

Benzo(a)pyrene (BP), benzo(a)pyrene 4,5-oxide (BP 4,5-ox-

ide), benzo(a)pyrene 7,8-oxide (BP 7,8-oxide), benzo(a)pyrene 9,10-oxide (BP 9,10-oxide), and benzo(a)pyrene 11,12-oxide (BP 11,12-oxide) were tested for carcinogenicity in newborn Swiss Webster mice by ip injection on postnatal days 1, 8, and 15 (200, 400, and 800 nanomoles, respectively). Mice that died after weaning or were sacrificed at 24 wk of age were autopsied. Three of 42 control mice had pulmonary adenomas with an av of 0.08 adenoma/mouse. Twenty-six of 32 mice treated with BP, 38/55 treated with BP 7,8-oxide, 13/67 treated with BP 11,12-oxide, and 4/47 treated with BP 4,5-oxide had pulmonary adenomas with an av of 10.0, 2.1, 0.32 and 0.10 adenoma/mouse, respectively. None of the mice treated with BP 9,10-oxide developed pulmonary adenomas. One mouse treated with BP 7,8-oxide developed an adenocarcinoma at 24 wk of age, and 13% of the mice treated with BP developed malignant lymphomas. The moderate tumorigenic activity of BP 7,8-oxide, together with earlier data on the strong carcinogenicity of benzo(a)pyrene 7,8-dihydrodiol, supports the view that BP 7,8-oxide is a proximate metabolite of BP in the newborn mouse. (23 refs)

- 79-0898 Dose-dependent Preferential Binding of Polycyclic Aromatic Hydrocarbons to Reiterated DNA of Murine Skin Cells in Culture.** (Eng) Shoyab, M. (Meloy Labs., Inc., 6715 Electronic Dr., Springfield, VA, 22151). *Proc Natl Acad Sci USA* 75(12): 5841-5845; 1978.

The distribution of the active metabolites of dimethylbenzo(a)anthracene (DMBA), benzo(a)pyrene (BP), and 3-methylcholanthrene (3-MC) bound to reiterated or unique regions of murine DNA was studied by a DNA-DNA renaturation technique. Murine epidermal cells isolated from the skins of newborn NIH Swiss mice were exposed to ³H-labeled DMBA (0.01-10 μ Ci/ml), BP (1 μ Ci/ml) or 3-MC (1 μ Ci/ml), and the hydrocarbon-labeled DNA was subsequently isolated, mixed with unlabeled normal DNA, and fragmented. Fragments were denatured, reassociated, and fractionated on hydroxyapatite according to their reassociation rates, and the specific activity of single- and double-stranded DNA was determined. At high concentrations of the three carcinogens, the active metabolites appeared to bind to DNA of different repetition frequencies at random. At lower doses, however, they bound preferentially to reiterated DNA sequences in a dose-dependent fashion. Thermal denaturation studies also indicated that ultimate carcinogens bound more to reiterated than single-copy DNA sequences at lower doses. An inverse linear relationship appeared to exist between this enrichment of hydrocarbon adducts in reiterated DNA sequences and the logarithm of the amount of total hydrocarbon bound to DNA. These studies suggest that at very low doses, similar to the constant low levels in the human environment, the intragenomic distribution of polycyclic aromatic hydrocarbons in cellular DNA appears to occur in a nonrandom fashion. (32 refs)

- 79-0899 Alteration of Collagen Synthesis in Chemical Carcinogenesis (Meeting Abstract).** (Eng) Hus-

sain, M. Z. (Sch. Dentistry, Univ. California, San Francisco, CA, 94132); Tolentino, M.; Belton, J. C.; Lee, S. D.; Bhatnagar, R. S. *J Dent Res* 58(Special A): 108; 1979. (no refs)

- 79-0900 Comparison of the Metabolic Profiles of Benzo(a)pyrene Obtained from Primary Cell Cultures and Subcellular Fractions Derived from Normal and Methylcholanthrene-induced Rat Liver.** (Eng) Schmeltz, I. (Naylor-Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595); Tosk, J.; Williams, G. M. *Cancer Lett* 5(2): 81-89; 1978.

Benzo(a)pyrene (BP) metabolite profiles produced by hepatocyte primary cell (HPC) cultures and isolated rat liver microsomal (9,000 x g) fractions, both derived from methylcholanthrene (MC)-induced or noninduced (normal) livers of male Fischer rats, were compared. The HPC cultures, both induced and noninduced, actively metabolized BP over a 24-hr period, generating metabolites that were extractable with organic solvents and easily monitored by high-pressure liquid chromatography. In both cases, the BP metabolites (the usual phenols, diols, and quinones) were qualitatively similar to those produced by the microsomal fractions. The HPC system also produced some unidentified metabolites that were found primarily in peak effluents eluting before the 9,10-diol peak. The metabolite profiles of the HPC cultures changed with time. In cells from noninduced livers, the 3- and 9-hydroxy-BP and the 9,10-, 4,5-, and 7,8-diol levels increased over 24 hr, but in cells from induced livers, the diol levels decreased markedly after 8 hr. This suggests that MC induction of the HPC culture enhances both the activation and, to a greater extent, the conjugative-detoxification pathways of BP. Therefore, in cells from induced livers, the formation of water-soluble metabolites is enhanced and levels of ethyl acetate-soluble metabolites are lower. The metabolism of BP in HPC culture is thus similar to the in vivo metabolism of the carcinogen but different from the microsomal metabolism of BP, in which conjugative-detoxification pathways are virtually inoperative, even with enzyme induction. (18 refs)

- 79-0901 Quantitative and Qualitative Changes in the Metabolism of Benzo(a)pyrene in Rat Tissues after Intragastric Administration of TCDD.** (Eng) Uotila, P. (Dept. Physiology, Univ. Turku, SF-20520 Turku 52, Finland); Parkki, M. G.; Aitio, A. *Toxicol Appl Pharmacol* 46(3): 671-683; 1978.

The effect of pretreatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, 20 μ g/kg given intragastrically 1 wk before sacrifice) on the in vitro metabolism of benzo(a)pyrene (BP) by liver, lung, and kidney preparations from Wistar and

Gunn (deficient in glucuronide conjugation) rats was studied. TCDD greatly increased the metabolism of BP to ethyl acetate-soluble metabolites by liver homogenates and microsomes. The increase was greatest in the case of unidentified "near origin" metabolites. 4,5-Dihydrodiol was the major metabolite formed by control liver preparations, whereas the 9,10- and 7,8-dihydrodiols were the major metabolites formed after TCDD treatment. TCDD pretreatment also drastically increased the metabolism of BP to water-soluble metabolites and significantly increased the liver microsomal protein content in Wistar, but not Gunn, rats. The increase in the amounts of phenols and quinones after TCDD treatment was much less pronounced. TCDD greatly increased the metabolism of BP to dihydrodiols, phenols, and unidentified metabolites by kidney and lung microsomes; the increase was greater with kidney microsomes from Gunn rats than with those from Wistar rats. TCDD treatment decreased the protein content of the kidney, and it had no effect on the metabolism of BP to water-soluble metabolites by kidney microsomes. The amount of BP metabolites covalently bound to liver, but not kidney or lung, microsomes was increased by TCDD pretreatment. (35 refs)

79-0902 A Short-Term Test to Detect Organotropic Specificity of Carcinogens. (Eng) Inui, N. (Section Cell Biology and Cytogenetics, Biological Res. Center, Japan Tobacco and Salt Public Corp., Hatano, Kanagawa 257, Japan); Nishi, Y. *Toxicol Lett* 2(5): 277-283; 1978.

A short-term screening method for detecting the organotropism of carcinogens was developed using an in vivo-in vitro combination assay. Induction of transformation, mutation, and chromosome aberrations was determined in cultured embryo cells derived from pregnant Syrian golden hamsters that had been injected ip on the 11th or 12th day of pregnancy with 200 mg/kg benzo(a)pyrene (BP), 200 mg/kg dimethylnitrosamine (DMN), or 100 mg/kg N-nitrosomethylurea (NMU). After BP treatment, morphological transformations were observed in lung and total body cells at rates of 3.70% and 1.45%, respectively. BP also caused chromosome aberrations and a 30.0- and 13.6-fold increase in 8-azaguanine (8AG)-resistant mutation in lung and total body cells, respectively. With DMN, the highest rates of morphological transformation (6.53%) and 8AG-resistant mutation (128/10⁷ cells) were induced in liver cells; chromosome abnormalities were detected in liver and total body cells. NMU caused a marked increase in morphological transformation (4.08% and 4.40%) and 8AG-resistant mutations (134.8/10⁷ and 79.9/10⁷ cells) in brain and total body cells, respectively. These results demonstrate that BP, DMN, and NMU cause chromosomal aberrations, 8AG-resistant mutation, and morphological transformation of cells from specific organs. Since cells cultured from whole embryos gave a positive result, the unknown tissue specificity of a carcinogen need not present an obstacle to an in vivo-in vitro test. (24 refs)

79-0903 Differences in the Repair of DNA Strand Breaks Induced by 9-Hydroxybenzo(a)pyrene and trans-7,8-Dihydro-7,8-dihydroxybenzo(a)pyrene in Cultured Human Fibroblasts. (Eng) Nordenskjold, M. (Dept. Clinical Genetics, Karolinska Institutet, S-104 01 Stockholm 60, Sweden); Soderhall, S.; Moldeus, P.; Jernstrom, B. *Biochem Biophys Res Commun* 85(4): 1535-1541; 1978.

The induction of strand breaks in human fibroblast DNA by 9-hydroxybenzo(a)pyrene (9-OH-BP) and trans-7,8-dihydro-7,8-dihydroxybenzo(a)pyrene (BP 7,8-dihydrodiol) and the kinetics of their repair were studied. The fibroblasts were incubated with 30 μ M 9-OH-BP or 10 μ M BP-7,8-dihydrodiol, washed after 30 min, and incubated in fresh medium. Incubation with either agent caused a rapid increase in DNA strand breaks. However, DNA strand breaks induced by 9-OH-BP were repaired within 2 hr of changing the medium, while those induced by BP 7,8-dihydrodiol were present for at least 6 hr. When fibroblasts were incubated with rat liver microsomes and an NADPH-generating system, there was an increased level of strand breaks at 30 min but the repair pattern was generally the same as that in incubations without microsomes. These results correlate well with results from mutagenicity test systems, in which 9-OH-BP is less active than the highly mutagenic BP 7,8-dihydrodiol. The results suggest that binding of activated BP 7,8-dihydrodiol to DNA gives rise to damage that is repaired less efficiently than damage caused by 9-OH-BP. These differences may be responsible for the marked differences in mutagenicity and carcinogenicity between 9-OH-BP and BP 7,8-dihydrodiol. (23 refs)

79-0904 A Human Plasma Component That Binds Benzo(a)pyrene. (Eng) McKenzie, M. (Dept. Biology, North Texas State Univ., Denton, TX, 76203); McLeMORE, T.; Rankin, P.; Martin, R. R.; Wray, N.; Cantrell, E.; Busbee, D. *Cancer* 42(6): 2733-2737; 1978.

Plasma, cultured lymphocytes, and fresh surgically excised lung tissue from smokers and nonsmokers and from smokers with and without primary squamous cell carcinoma of the lung were examined in an attempt to identify a cytoplasmic receptor molecule for benzo(a)pyrene (BP). A component capable of binding BP was measured in plasma from cigarette smokers and nonsmokers. This plasma fraction was found to have a high specificity of binding to BP, it bound benzanthracene competitively with BP, and it was positively correlated ($r = 0.861$, $p < 0.001$) with the capacity of the individual subject's lymphocytes to be induced for AHH activity in culture. The inverse correlation ($r = -0.957$, $p < 0.001$) found between the presence of the plasma component in lung cancer patients and the capacity of their lymphocytes to be induced in culture cannot be explained at this time. A BP-binding fraction was not found in induced or uninduced cultured lymphocytes from smokers or nonsmokers or in homogenates of

lung excisional tissue from smokers with or without primary lung cancer. (29 refs)

- 79-0905 Quantitative Determination of Benzo(a)pyrene in Foodstuffs Using Benzo(a)pyrene[G-³H].** (Jpn) Masuda, Y. (Daiichi Coll. Pharmaceutical Sciences, 93 Tamagawa-cho, Minami-ku, Fukuoka, Japan); Shimamura, K.; Yano, H. *J Food Hyg Soc Jpn* 18(4): 362-367; 1977.

A method for determining nanogram quantities of benzo(a)-pyrene (BP) in foodstuffs using ³H-BP is described. Foodstuff extracts to which ³H-BP was added were separated by column chromatography on Florisil and by thin-layer chromatography on acetylated cellulose. The concentration and radioactivity of BP in the final fraction were determined by fluorescence spectrometry and liquid scintillation counting. The concentration of BP in the analyzed sample was calculated from the amount of BP isolated and the recovery ratio. For a 50-g sample, measurements were accurate at levels >0.5 ppb; a wide variance occurred at levels <0.2 ppb. The method was then applied to various food samples. The av quantity of BP found in Tempura oil, salad oil, wheat flour, and polished (white) rice was 0.6, 0.2, 0.1, and <0.1 ppb, respectively. (17 refs)

- 79-0906 Analysis of Polycyclic Aromatic Hydrocarbon Air Pollutants by High-Pressure Liquid Chromatography.** (Hun) Morlin, Z. (Orszagos Kozegeszsegugyi Intezet, Budapest, Hungary); Kertesz, M.; Kiss, A. M. *Egeszsegtudomany* 22(4): 370-378; 1978.

The quantitative determination of six polycyclic aromatic hydrocarbon environmental pollutants in standard air mixtures and in various environmental samples was made by high-pressure liquid chromatography (HPLC). The air, dust, soot, and snow samples were extracted with benzol and purified by chromatography prior to HPLC. The presence of anthracene, chrysene, pyrene, fluoranthene, benzo(a)pyrene, and 3-methylcholanthrene in various combinations was demonstrated. (14 refs)

- 79-0907 Benzo(a)pyrene Determination in Airborne Soot from Metallurgical Factories.** (Ger) Masek, V. (Na valse 4, 70200 Ostrava-Privaz, Czechoslovakia). *Zentralbl Arbeitsmed Arbeitsschutz Proph* 28(6): 168-170; 1978.

Benzo(a)pyrene (BP) levels in 291 samples of airborne soot and smoke from four types of steel-producing operations were determined. The av airborne BP levels (in micrograms/gram) found near the coking of bituminous coal was 276; near coke ovens producing pitch, 989; near blast furnaces, 9.4; and

near steel production, 11.3. The first two processes expose the worker to dangerous levels of BP. (6 refs)

- 79-0908 Correlation of the Inhibition by Retinoids of Tumor Promoter-induced Mouse Epidermal Ornithine Decarboxylase Activity and of Skin Tumor Promotion.** (Eng) Verma, A. K. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706); Shapas, B. G.; Rice, H. M.; Boutwell, R. K. *Cancer Res* 39(2, Part 1): 419-425; 1979.

Effects of retinoic acid (RA) and several synthetic retinoids on induction of epidermal ornithine decarboxylase (ODC) activity and formation of skin papillomas promoted with 12-O-tetradecanoylphorbol-13-acetate (TPA) were studied in female Charles River CD-1 mice. Tumors were initiated in all mice by topical application of 0.2 micromole of dimethylbenz(a)anthracene (DMBA) in acetone followed 14 days later by TPA promotion [8 or 17 nanomoles (nmol)] 2x/wk for the duration of the experiment. Various retinoids were administered to mouse skin 1 hr before each TPA treatment. Multiple applications (6-11) of TPA increased ODC activity approx 600-fold, but pretreatment with 1.7 nmol RA inhibited ODC activity 60%-80%, and pretreatment with 1.7 or 17 nmol RA reduced the number of papillomas/mouse by 57% and 75%, respectively. Skin tumor development was not altered by administering RA 24 hr after TPA treatment or at various times before tumor initiation by DMBA. Pretreatment with the trimethylmethoxyphenyl analog of ethyl retinoate, 13-cis-retinoic acid, or the dimethylmethoxyethylcyclopentenyl analog of RA inhibited TPA-induced ODC activity, the number of papilloma-bearing mice, and the number of papillomas/mouse. The trimethylhydroxyphenyl and 13-trifluoromethyltrimethylmethoxyphenyl analogs of ethyl retinoate did not alter these parameters. Although retinoid treatment inhibited ODC activity and the resultant increases in putrescine levels, it did not alter TPA-induced S-adenosyl-L-methionine decarboxylase activity or the accumulation of spermidine and spermine. These findings indicate that RA exerts its prophylactic effect by interfering with promotion and not by inhibiting initiation or inactivating initiated cells. (35 refs)

- 79-0909 Retinoids Induce Sister-Chromatid Exchanges In Human Diploid Fibroblasts.** (Eng) Juhl, H. J. (I. Medizinische Klinik, Universitat Hamburg, Martinistrasse 52, 2000 Hamburg 20, W. Germany); Schurer, C. C.; Bartram, C. R.; Kohl, F. V.; Melderis, H.; von Wichert, P.; Rudiger, H. W. *Mutat Res* 58(2/3): 317-320; 1978.

In view of the contradictory results obtained in carcinogenicity studies with retinoids, experiments were conducted to determine whether these compounds induce sister chromatid

exchanges (SCE) in cultured human diploid fibroblasts. Vitamin A palmitate, retinoic acid, and the retinoic acid analog ethyl all-trans-9- (4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoates (Ro 10-9359) were incubated with fibroblasts (3×10^5 cells) from five healthy individuals in the presence of bromodeoxyuridine (1 or 3 mg/ml) for 72 hr and analyzed for SCE by fluorescence microscopy. All three compounds more than doubled the rate of SCE, causing a max plateau of approx 14 SCE/metaphase. However, the dose of vitamin A palmitate (approx 50 μ g/ml) required to achieve this plateau was 10 times that necessary to cause a similar max by the other two compounds tested. The dose related induction of SCE by a retinoid was apparently unrelated to its previously reported antineoplastic activity. (18 refs)

79-0910 Increased Aryl Hydrocarbon Hydroxylase Activity in Hepatic Microsomes from Streptozotocin-Diabetic Female Rats. (Eng) Reinke, L. A. (Dept. Biomedical Chemistry, Coll. Pharmacy, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105); Stohs, S. J.; Rosenberg, H. *Xenobiotica* 8(12): 769-778; 1978.

Alterations of hepatic microsomal aryl hydrocarbon hydroxylase (AHH) activity were studied in Sprague-Dawley rats and Swiss Webster mice with streptozotocin (STZ)-induced diabetes (60 and 200 mg/kg iv, respectively). AHH activity was decreased 70% in diabetic male rats but it was increased 75% over control values in diabetic female rats. Insulin treatment of both sexes returned AHH values to control levels. In both male and female diabetic mice AHH activity was 65%-70% higher than that in controls. In female rats, a transient hyperglycemia occurred 4 hr after STZ injection that decreased by 9 hr. At 24 hr after STZ treatment, however, a severe hyperglycemia developed that persisted throughout the study. AHH activity did not increase until 96 hr after injection, and it peaked at 7 days. Cytochrome P-450 levels began to increase at 48 hr to a max at 96 hr. Nicotinamide pretreatment (1,000 mg/kg, ip) of female rats 15 min before STZ injection protected them from the diabetogenic effects of STZ and also prevented the increase in AHH activity. Treatment of control and diabetic female rats (the latter 7 days after STZ) with 3-methylcholanthrene (20 mg/kg/day \times 3, ip) resulted in a larger increase in AHH activity in the former (3.04 and 2.27 units, respectively, vs an untreated control value of 0.30), but similar increases in cytochrome P-448 levels in both. Addition of SKF 525-A, metyrapone, and rotenone to hepatic microsomes of control and diabetic female rats in vitro resulted in differential stimulatory or inhibitory effects on AHH activity. In contrast, α -naphthoflavone (an inhibitor of cytochrome P-448-dependent reactions) produced similar stimulatory responses in microsomes from both rat groups, which suggests that cytochrome P-448 is not involved in the enhanced AHH activity observed in diabetic females. It is concluded that

there is a sex-dependent effect of STZ-induced diabetes on AHH activity in rats. (43 refs)

79-0911 Studies on the Induction of Sister Chromatid Exchange in Human Fibroblasts by Diethylstilbestrol (Meeting Abstract). (Eng) Haensch, F. T. (I. Medizinische Klinik, Univ. Hamburg, Hamburg, W. Germany); Rudiger, H. W. *Clin Genet* 14(5): 291-292; 1978. (4 refs)

79-0912 Cancer Development in Male Reproductive Tract in Rats Given Diethylstilbestrol at Neonatal Age. (Eng) Arai, Y. (Dept. Anatomy, Juntendo Univ. Sch. Medicine, Hongo 2-1-1, Bunkyo-ku, Tokyo 113, Japan); Chen, C. Y.; Nishizuka, Y. *Gann* 69(6): 861-862; 1978.

The effect of daily administration of diethylstilbestrol (DES, 1 μ g sc for first 10 days after birth, 2 μ g for days 10 to 20, and 4 μ g for days 20 to 30) on castrated and intact male Wistar rats was studied. The surface epithelium of the coagulating gland (CG) and ejaculatory duct (ED) showed profound squamous metaplasia in the DES-treated rats. The lumina of the CGs and EDs of the castrated rats were distended by masses of sloughed and cornified cells, and extensive downgrowths and papillary outgrowths of epithelial cells appeared to progress with age. Highly invasive squamous cell carcinomas developed in the CG, ED, and dorsolateral prostate of two castrated rats. Metaplastic changes without downgrowth or outgrowth proliferations of the epithelium were observed in the intact animals. The data indicate a possible correlation between neonatal DES treatment and cancer and suggest the importance of follow-up studies in human males exposed prenatally to DES. (6 refs)

79-0913 Peroxidase-mediated Oxidation, a Possible Pathway for Metabolic Activation of Diethylstilbestrol. (Eng) Metzler, M. (Inst. Toxicology, Univ. Wurzburg, Versbacher Strasse 9, D-8700 Wurzburg, W. Germany); McLachlan, J. A. *Biochem Biophys Res Commun* 85(3): 874-884; 1978.

The oxidation of diethylstilbestrol in the presence of peroxidase preparations from horseradish or mouse uterus, hydrogen peroxide, and either DNA or albumin yielded one or more compounds that interacted with the DNA and albumin. The oxidation reaction appeared to involve the semiquinone and quinone of DES, as demonstrated by nonextractable binding to DNA and bovine serum albumin. Analysis of ether extracts of the complete incubation systems by radio-gas liquid chromatography revealed at least six peaks, three of which were identified as cis- and trans-DES and β -dienestrol

by cochromatography with reference compounds. The peroxidase-mediated binding of DES to DNA and proteins may have relevance for the mechanism by which DES exerts its toxicity. Peroxidase activity is preferentially found in tissues depending on estrogens for growth. Thus, peroxidase-mediated oxidation of DES and binding to DNA can take place in estrogen target organs, which could explain in part the organotropic toxicity of DES. (29 refs)

- 79-0914 The Metabolism of Diethylstilbestrol in the Rhesus Monkey and Chimpanzee.** (Eng) Helton, E. D. (Natl. Center Toxicological Res., Food and Drug Admin. DHEW, Jefferson, AR, 72079); Hill, D. E.; Lipe, G. W.; Szisak, T. J.; King, J. W. *J Environ Pathol Toxicol* 2(2): 521-537; 1978.

To study diethylstilbestrol (DES) metabolism, various doses of radiolabeled DES were administered po or iv to one pregnant and three nonpregnant female rhesus monkeys and to one nonpregnant female chimpanzee. The principal mode of excretion of both tritiated and ^{14}C -DES, regardless of route of administration, was in the urine of both species. The radioactive material in the urine was not extractable with benzene, and the urinary conjugate profiles were similar for all animals. The urine contained no nonpolar radioactivity, and Sephadex LH-20 chromatography [methanol/ethanol (50:50)] resolved the radioactivity into five fractions, A-E. A-D were hydrolyzable with β -glucuronidase, and the principal aglycones were identified by gas chromatography/mass spectrometry (GD/MS) as cis-trans DES and dienestrol. The fecal excretory products were extracted with dimethoxymethane/methanol (50:50), and the radioactivity was partitioned between benzene and water. The polar radioactivity was resolved by LH-20 into chromatographic fractions similar to those of the urinary conjugates. However, these fecal conjugates were less sensitive to β -glucuronidase hydrolysis. The primary nonpolar fecal radioactivity was chromatographically similar to DES in both species, and in the rhesus monkey the principal products identified were cis-trans DES and dienestrol. (28 refs)

- 79-0915 Study on the Mutagenicity of Conjugated Estrogens in Human, Animal and Bacterial Systems.** (Eng) Sirianni, S. R. (Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263); Hale, P.; Brown, M.; Huang, C. C.; Paigen, B.; Ambrus, J. L. *J Med Clin Exp Theor* 9(5): 423-432; 1978.

The direct mutagenic effect of conjugated estrogens (Premarin) was studied in bacterial and mammalian systems, includ-

ing normal and neoplastic human cell lines. Two strains of *Salmonella typhimurium* (TA100 and TA98), 2 normal human lymphoid cell lines, 3 lymphoid cell lines from patients with Burkitt's lymphoma (B-35 M, HRIK, and Raji), and 1 Chinese hamster cell line (V-79) were exposed continuously to estrogens at 50 $\mu\text{g}/\text{ml}$. Following colcemid treatment, metaphases were studied for chromosome lesions. Diffusion chamber cultures were established and implanted into the abdominal cavity of mice. Three days later, the animals were injected ip with 25-400 $\mu\text{g}/\text{g}$ of estrogens. Cell viability, number, and cytogenic characteristics were determined following colchicine injection into the chambers. There were no significant increases in mutation rate or chromosome aberrations after exposure of the test material to the conjugated estrogens. (37 refs)

- 79-0916 Primary and Transplantable Adenocarcinomas of the A x C Rat Ventral Prostate Gland: Morphologic Characterization and Examination of C_{19} -Steroid Metabolism by Early-Passage Tumors.** (Eng) Shain, S. A. (Southwest Foundation Res. and Education, P.O. Box 28147, San Antonio, TX, 78284); McCullough, B.; Nitchuk, W. M. *J Natl Cancer Inst* 62(2): 313-322; 1979.

Spontaneous adenocarcinomas of the ventral prostate glands in 23/33 aged (30-46 mo old) virgin male A x C rats are described. Eleven of the 23 tumor-bearers had received a single im injection of 15 mg testosterone-p-hexoxyphenyl propionate (Andradurin). Multiple acini and focal atypical hyperplasia were common morphologic features of the adenocarcinomas, which were bilateral in six rats. Atypical hyperplasia of ventral prostate acinar epithelium was found in atrophic as well as neoplastic epithelium. It consisted of thickened epithelium in which various numbers of cells had a swollen, foamy, PAS-positive cytoplasm and condensed, eccentric nuclei. Andradurin treatment caused the development of columnar epithelium in many ventral prostate acini, increased the frequency of adenocarcinoma, and amplified the anaplastic character of the neoplastic cells. Although no evidence of metastasis was seen, prostate adenocarcinomas obtained from 2/4 Andradurin-treated rats produced transplantable tumors when injected sc into syngeneic recipients. The histologic features of these tumors were comparable to the primary lesions from which they were derived. The transplantable adenocarcinomas metabolized testosterone predominantly to 17-ketosteroids, which accounted for 61% to 73% of the elaborated metabolites. The principal metabolite, 4-androstenedione, represented 48%-61% of the total metabolic products. Concomitantly, 5 α -reduced 17 β -hydroxysteroid production decreased. Most acid phosphatase activity of the transplantable adenocarcinoma was tartrate-inhibitable. These studies indicate that the aged male A x C rat offers an opportunity to study the pathogenesis of prostate neoplasia without the application of carcinogens. (29 refs)

79-0917 In Vitro Effects of Hormonal Stimuli upon Tyrosinase and Peroxidase Activities in Murine Melanomas. (Eng) Abramowitz, J. (Dept. Biology, Wayne State Univ., Detroit, MI, 48202); Chavin, W. *Biochem Biophys Res Commun* 85(3): 1067-1073; 1978.

Changes in tyrosinase and peroxidase activities in murine melanomas in response to ACTH and corticosterone (CS) were compared in vitro. B-16, Cloudman S-91, and Harding-Passey (HP) melanoma dices were treated with ACTH (100 mIU/ml) and/or CS hemisuccinate (50 µg/ml). The incubates were terminated at seven intervals (5-240 min), and the enzyme activities were determined. ACTH and CS altered tyrosinase activity in all three melanomas but not in any consistent pattern, in some cases stimulating activity, in other cases depressing it, depending on the time interval studied. ACTH + CS produced an early peak in tyrosinase activity in all three tumors; it was observed at 15 min in the B-16 and S-91 melanomas and at 30 min in the HP melanoma. Activity decreased subsequent to this peak; a second higher peak occurred at 240 min in the S-91 and HP melanomas. There were no changes in peroxidase activity following hormone treatment. Tyrosinase activity, but not peroxidase activity, was correlated with the amount of melanin in the melanomas. It is concluded that tyrosinase is the enzyme of physiological importance in the regulation of melanin pigmentation. (35 refs)

79-0918 On the Biological Activity of Estrone In Vivo. (Eng) Thijssen, J. H. (Dept. Endocrinology, Univ. Hosp., Catharijnesingel 101, Utrecht, Netherlands); Wiegerinck, M. A.; Mulder, G.; Poortman, J. *In: Front Horm Res* 5: 220-229; 1978.

Estrogen levels in the myometrium and endometrium of six postmenopausal women were measured and compared with levels in peripheral blood after a 12-hr infusion of 4 µCi/hr ³H-estrone (total dose, approx 0.3 µg estrone). Infusion and sampling were done in conjunction with a hysterectomy performed on all women for nononcological reasons. Protein-bound radioactive estrogens in tissue were measured by a combination of thin-layer chromatography, gas-liquid chromatography, and liquid scintillation counting. In three patients, the ³H-estrone/³H-estradiol ratio was much greater in the tissues (bound to protein in cytosol) than in the plasma. This increase was not seen in the fourth patient, the only one who displayed premenopausal estrogen concentrations in blood, indicating a production of estradiol in addition to the conversion of estrone to estradiol. In the fifth patient, in whom the infusion was stopped 2 hr before hysterectomy (because of mechanical problems), the increase in estradiol concentration of the receptor-bound radioactivity was even more marked. In the sixth patient, the level of receptor-bound estrogens in the nucleus and that of nonreceptor-bound estrogens in the cytosol and nuclei could also be obtained. The

observed high ratio in the nuclear-bound fractions confirmed the previously documented results. Local factors favoring the formation of estradiol from estrone in the cells of the uterus may explain the differential in estrone/estradiol ratios between peripheral blood and uterine tissue. The relation between certain malignancies and an increased estrone production is probably due to an increased biological activity of estrogens rather than to specific separate effects of estrone. (11 refs)

79-0919 Spontaneous Rupture of a Liver Adenoma Following Long-Term Use of Oral Contraceptives. (Ger) Pollak, H. (Chirurgische Klinik, Stadt. Krankenhaus, D-7730 Villingen-Schwenningen, W. Germany). *Munch Med Wochenschr* 121(3): 93-94; 1979.

Hepatocellular adenoma of the liver with hepatic peliosis was found in a 34-yr-old woman who had been using oral contraceptives (0.5 mg Norgestrel and 0.05 mg ethinyl estradiol) for the last 10 yr without interruption. The adenoma ruptured spontaneously. (17 refs)

79-0920 Mesonephric Tumor of the Cervix Uteri in Infancy. (Ger) Scharli, A. F. (Kinderchirurgische Abteilung, Kinderspital, CH-6004 Luzern, Switzerland); Gnös, P.; Laissue, J. *Z Kinderchir* 25(2): 164-169; 1978.

Two cases of mesonephric tumor of the uterine cervix in young girls (2 and 3 yr old) are presented. The mother of the first patient had been treated at the end of the first trimester for threatened miscarriage with six injections of estrogen and six of progesterone. Colposcopy is valuable for determining the cause of vaginal bleeding in children. Any history of hormonal treatment of the mother during pregnancy should be recorded. (11 refs)

79-0921 Cancer of the Prostate and Breast. (Por) de A. Rocha, L. C. (Santa Casa da Misericórdia de Curitiba, Curitiba, PR, Brazil); Rocha, J. A. *J Bras Urol* 4(3): 218-220; 1978.

Prostatic adenocarcinoma was diagnosed in a 84-yr-old man. He received hormone treatment with ethylstilbestrol diphosphate (1.5 g/day, total dose 18 g) and estradiol valerianate (Primogyna Depot im, dose not given). He developed first bilateral gynecomasty and eventually ductal carcinoma of the breast 2 yr after the diagnosis of the prostatic adenocarcinoma. (7 refs)

79-0922 Influence of Low-dose Mutagen Exposure on the Association of Human Acrocentric Chromosomes (Meeting Abstract). (Eng) Hens, L. (Inst. Morphology, Lab. Anthropogenetics, Free Univ. Brussels, Brussels, Belgium); Kirsch-Volders, M.; Verschaeve, L.; Alexander, A.; Driesen, M.; Poma, K.; Susanne, C. *Clin Genet* 14(5): 293-294; 1978. (no refs)

resembled that of normal liver, but there were no portal tracts or bile ducts. (15 refs)

79-0923 An Androgen-associated Hepatic Adenoma in a Transsexual. (Eng) Coombes, G. B. (Addenbrooke's Hosp., Hills Road, Cambridge, England); Reiser, J.; Paradinas, F. J.; Burn, I. *Br J Surg* 65(12): 869-870; 1978.

A full report is given of the first case of a hepatic adenoma developing in a female-male transsexual (aged 27 yr) who had been taking methyltestosterone (50 mg tid) for 3 yr. α -Feto-protein and carcinoembryonic antigen levels were elevated in this patient. The trabecular arrangement of the tumor cells

See also:

- *(Rev.): 79-0601, 79-0602, 79-0603, 79-0604, 79-0605, 79-0606, 79-0607, 79-0608, 79-0609, 79-0610, 79-0611, 79-0612, 79-0613, 79-0614, 79-0619, 79-0624, 79-0636, 79-0637, 79-0638, 79-0639.
- *(Phys.): 79-0924, 79-0925, 79-0926, 79-0927, 79-0932, 79-0939, 79-0942, 79-0943.
- *(Viral): 79-0972, 79-0979, 79-0984, 79-0989, 79-1012.
- *(Path.): 79-1099, 79-1110.
- *(Epid-Biom.): 79-1133, 79-1137, 79-1141, 79-1142, 79-1143, 79-1145, 79-1149, 79-1151, 79-1152, 79-1156, 79-1162, 79-1163, 79-1164, 79-1165, 79-1170, 79-1171, 79-1176, 79-1178.

PHYSICAL CARCINOGENESIS

79-0924 DNA Repair In Xeroderma Pigmentosum Cells Treated with Combinations of Ultraviolet Radiation and N-Acetoxy-2-acetylaminofluorene. (Eng) Ahmed, F. E. (Dept. Biology, Brookhaven Natl. Lab., Upton, NY, 11973); Setlow, R. B. *Cancer Res* 39(2, Part 1): 471-479; 1979.

Excision repair was examined in three normal human fibroblast lines and a xeroderma pigmentosum (XP) variant (excision repair-proficient) and in XP types C, D, and E (excision repair-deficient) after they were treated with UV irradiation (254 nm) and/or N-acetoxy-2-acetylaminofluorene (AAAF). Three quantitative techniques were used: unscheduled DNA synthesis measured radioautographically, the photolysis of 5-bromo-2'-deoxyuridine (BrdUrd) incorporated into parental DNA during repair, and the loss of sites (pyrimidine dimers) sensitive to a UV endonuclease. Saturation doses of 20 joules UV/m² and 30 mM AAAF were used for combined treatments. The three techniques gave similar results. In repair-proficient cells, total repair was additive. In repair-deficient XP cells total repair was much less than additive and AAAF inhibited the excision of pyrimidine dimers. It is concluded that pathways for the repair of UV- and AAAF-induced lesions are not identical in the repair-proficient cells and that in repair-deficient cells there is an inhibitory effect exerted by major or minor products of each agent on the repair enzyme(s) of the other. (45 refs)

79-0925 Effect of Acetoxyacetylaminofluorene on Transfection of *E. coli* by ϕ X-174 RF-DNA (Meeting Abstract). (Eng) Taylor, W. D. (Pennsylvania State Univ., University Park, PA, 16802); Deering, R. A.; Tsai, C. L. *Biophys J* 25(2, part 2): 220a; 1979. (no refs)

79-0926 DNA Repair in Xeroderma Pigmentosum Heterozygotes (Meeting Abstract). (Eng) Setlow, R. B. (Brookhaven Natl. Lab., Upton, NY, 11973); Grist, E. *Biophys J* 25(2, part 2): 155a; 1979. (1 ref)

79-0927 Lesions Induced in Deoxyribonucleic Acid by Benzo(a)pyrene and Near Ultraviolet Light (Meeting Abstract). (Eng) Strniste, G. F. (Cellular and Molecular Biology Group, Los Alamos Scientific Lab., Univ. California, Los Alamos, NM, 87545); Martinez, A. M.; Martinez, E. M. *Biophys J* 25(2, part 2): 220a; 1979. (no refs)

79-0928 Host Cell Reactivation of *B. subtilis* Bacteriophages ϕ 29 and SPO2-c12 (Meeting Abstract). (Eng) Pepper, W. L. (Dept. Microbiology, Clemson Univ., Clemson, SC, 29631); Larcom, L. L. *Biophys J* 25(2, part 2): 220a; 1979. (no refs)

79-0929 Monomerization of Pyrimidine Dimers in DNA by LYS-TRP-LYS: Only Short Wavelength Ultraviolet Radiation is Effective (Meeting Abstract). (Eng) Sutherland, J. C. (Dept. Biology, Brookhaven Natl. Lab., Upton, NY, 11973); Griffen, K. P. *Biophys J* 25(2, part 2): 154a; 1979. (2 refs)

79-0930 Correlation among the Rates of Dimer Excision, DNA Repair Replication and Recovery of Human Cells from Potentially Lethal Damage Induced by Ultraviolet Radiation (Meeting Abstract). (Eng) Konze-Thomas, B. (Michigan State Univ., East Lansing, MI, 48824); Levinson, J. W.; Maher, V. M.; McCormick, J. J. *Biophys J* 25(2, part 2): 155a; 1979. (no refs)

79-0931 Is Post-Replication Repair Real? (Meeting Abstract). (Eng) Cleaver, J. E. (Lab. Radiobiology, Univ. California, San Francisco, CA, 94143); Kapp, L.; Park, S. D. *Biophys J* 25(2, part 2): 156a; 1979. (no refs)

79-0932 Inhibition of DNA Excision Repair in Human Cells by Arabinofuranosyl Cytosine: Effect of Normal and Xeroderma Pigmentosum Cells (Meeting Abstract). (Eng) Dunn, W. C. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Regan, J. D. *Biophys J* 25(2, part 2): 156a; 1979. (no refs)

79-0933 Pattern of Ultra-violet-Light-induced Repair in Metaphase and Interphase Chromosomes. (Eng) Johnson, R. T. (Dept. Zoology, Univ. Cambridge, Downing St., Cambridge CB2 3EJ, England); Sperling, K. *Int J Radiat Biol* 34(6): 575-582; 1978.

The interchromosomal distribution of unscheduled DNA synthesis during the first hour of repair and its intrachromosomal location after UV irradiation (60 joules/m²) of cells arrested in metaphase were examined in heteroploid

HeLa cells and in three human diploid fibroblast cultures. The fibroblasts were obtained from a patient with Fanconi's anemia, a parent of a patient with xeroderma pigmentosum (ie, a xeroderma pigmentosum heterozygote), and a control with apparently normal repair capacity. The interphase chromosomes were visualized by cell fusion and the induction of premature chromosome condensation (PCC). The amount of unscheduled DNA synthesis among the chromosomes of each cell line was similar and was not affected by hydroxyurea (HU: 10^{-2} M). The intrachromosomal distribution of repair was nonrandom for each cell line, with a clear enrichment of label at the centromere and telomeres. The centromere-telomere (CT) pattern of repair was also observed in interphase chromosomes obtained from the G₂ nucleus. These results show that 50% of metaphase chromosome repair and 30% of G₂ chromosome repair is associated with 30% and 20% of the chromosome lengths, respectively. The data show that the amount of initial repair is proportional to chromosome length and therefore to DNA content. They also show that the CT pattern is not influenced by heteroploidy nor by the genetic disease Fanconi's anemia. (22 refs)

- 79-0934 Different Repairability of the Chromosomal and Cytoplasmic Deoxyribonucleic Acid in *Escherichia coli* Damaged by γ and Ultraviolet Irradiation.** (Eng) Petranovic, D. (Institute "Ruder Boskovic", P. O. Box 1016, 41001 Zagreb, Croatia, Yugoslavia); Petranovic, M.; Noznic, R.; Trgovcevic, Z. *Radiat Res* 76(3): 587-595; 1978.

The relative efficiencies with which chromosomal and extra-chromosomal DNA's are repaired in irradiated bacteria were determined by exposing repair-proficient *Escherichia coli* C600 cells lysogenic for, or infected with, the thermoinducible phage λ cI857 to γ or UV radiation, then testing them for colony- and plaque-forming ability. The bacteria were at most 5.3-fold more sensitive to γ rays and 1.5-fold more sensitive to UV light than phage that was irradiated and repaired in the cytoplasm or irradiated in the bacterial chromosome and repaired in the cytoplasm after heat induction. Since the bacterial DNA is about 80 times larger than the phage DNA, the difference in radiosensitivity between the bacterial cells and intracellularly irradiated phage may reflect a difference in repair of the chromosomal and cytoplasmic DNA. This view was supported by the observation that the absence of repair in the system *E. coli* AB2480 *uvrA recA*- λ cI857 *ind red* gave the expected ratio of 80:1 for the UV sensitivity of cells and that of intracellular phage. (32 refs)

- 79-0935 Dose Response Relations for UV Induction of Protein X in *E. coli* Strain AB1157 (Meeting Abstract).** (Eng) Kazanis, D. (Zoology Dept., Duke Univ., Durham, NC, 27706); Pollard, E. C.; Fluke, D. J. *Biophys J* 25(2, part 2): 157a; 1979. (no refs)

- 79-0936 Dose Response Relations for UV Induction of Septum Inhibition in Four Strains of *E. coli* K12 (Meeting Abstract).** (Eng) Robinson, B. (Duke Univ., Durham, NC, 27706); Fluke, D. J.; Pollard, E. C. *Biophys J* 25(2, part 2): 157a; 1979. (no refs)

- 79-0937 Ultraviolet Light Induces Epidermal Ornithine Decarboxylase Activity.** (Eng) Lowe, N. (Section Dermatology, Univ. Wisconsin, Madison, WI); Verma, A. K.; Boutwell, R. K. *J Invest Dermatol* 71(6): 417-418; 1978.

Changes in epidermal ornithine decarboxylase (ODC) activity after exposure to UV light (0.90 J/cm^2) were studied in female HKH/Hr hairless mice. ODC activity increased significantly 2 hr after UV exposure. A max eighty fold increase was observed 24 hr after UV exposure, the level of activity decreasing again at 48 hr. Epidermal DNA synthesis decreased significantly at 6 and 24 hr after UV exposure. It was significantly elevated 48 hr after exposure. The results indicate that polyamine biosynthetic enzyme activity precedes the delayed increase in epidermal DNA synthesis following UV exposure. (14 refs)

- 79-0938 Ultraviolet-Light Induced Transformation of Human Cells (Meeting Abstract).** (Eng) Sutherland, B. (Dept. Biology, Brookhaven Natl. Lab., Upton, NY, 11973); Oliver, R.; Gih, A.; Cimino, J. S. *Biophys J* 25(2, part 2): 87a; 1979. (no refs)

- 79-0939 8-Methoxypsoralen Induced Alterations of Mammalian Cells.** (Eng) Evans, D. L. (Dept. Microbiology and Immunology, Bowman Gray Sch. Medicine, Wake Forest Univ., Winston-Salem, NC, 27103); Morrow, K. J. *J Invest Dermatol* 72(1): 35-41; 1979.

In vitro and in vivo assays demonstrate that 8-methoxypsoralen, in the presence of UV light (8-MOP-UV), causes morphologic changes in cell growth characteristics and stimulates endogenous murine leukemia virus (MuLV) production in certain mammalian cells. Transformation for certain growth characteristics occurred in high percentages of 8-MOP-UV-treated primary mouse, rat, and hamster embryo cultures and in continuous cell lines (BHK₂₁/Cl₁₃, NIH/3T3, and BALB/c 3T3). Morphological alterations were observed at both macroscopic (focus formation) and microscopic (random growth patterns, multilayering, etc.) levels of examination. Treated cells that demonstrated altered phenotypes were tested for growth in soft agarose. Those cultures with altered morphology and whose cells grew in soft agarose were, in addition, tested for MuLV production by the XC cytopathogenicity test. 8-MOP-UV-transformed mouse, rat,

and hamster (except BHK₂₁/Cl₁₃) cells produced positive XC results. Fluorescent antibody tests of cells that produced giant cell cytopathogenicity were positive. Cytoplasmic fluorescence was observed when these cells were tested with antisera to oncornavirus group-specific (gs-3) antigen. Control untreated cells were negative in all experiments. Hamster embryo fibroblasts transformed with 8-MOP-UV acquired apparent unlimited in vitro growth characteristics (>150 population density levels); they exhibited mixoploidy; small numbers of these cells caused spindle cell sarcomas in hamster cheek pouches and produced tumors in newborn hamsters; and their generation times (mean, 22.5 hr) were characteristic of transformed cells. Expression of altered growth characteristics by BHK₂₁/Cl₁₃ cells may be related to selection for cytotoxicity-resistant cells rather than being caused by 8-MOP-UV-induced transformation. (39 refs)

79-0940 Relative Contribution of Unrepaired Single Strand and Double Strand DNA Breaks to Biological Damage (Meeting Abstract). (Eng) Cole, A. (Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Texas Medical Center, Houston, TX, 77030); Meyn, R. E.; Chen, R. *Biophys J* 25(2, part 2): 155a; 1979. (no refs)

79-0941 The Induction of Chromosomal Deletions in *Aspergillus nidulans* by Various Ionizing Radiations (Meeting Abstract). (Eng) Normansell, I. D. (Polytechnic Central London, London W1M 8JS, England); Holt, G. *Int J Radiat Biol* 34(6): 553; 1978. (no refs)

79-0942 Protease Inhibitors Suppress Radiation-induced Malignant Transformation In Vitro. (Eng) Kennedy, A. R. (Lab. Radiobiology, Dept. Physiology, Harvard Univ., Sch. Public Health, Boston, MA, 02115); Little, J. B. *Nature* 276(5690): 825-826; 1978.

The effects of antipain (AP) and leupeptin (LP) on radiation-induced and two-stage transformation in vitro were investigated in a C3H mouse embryo-derived cell line (10T 1/2 clone 8) or in a BALB/3T3 line (A31-11). In 10 1/2 cells, AP (50 µg/ml) suppressed x-ray-induced transformation, (600 rads) and completely abolished radiation transformation (400 rads) enhanced by 12-O-tetradecanoyl-phorbol-13-acetate (TPA, 0.1 µg/ml). LP (50 µg/ml) suppressed radiation transformation with and without TPA promotion, but it did not seem as effective as AP. In these experiments, AP and LP were present for the entire postirradiation expression period of 6 wk. AP at 1 mM reduced transformation from 2.0×10^{-3} to $< 3.2 \times 10^{-4}$ when present for 5 days and to 5.5×10^{-4} when present for only 1 day following 600 rads. AP also completely suppressed the transformation induced in A31-11 cells by 100 or 400 rads of x-rays plus TPA. The results offer

in vitro confirmation for the suppressive effect of protease inhibitors on carcinogenesis in vivo. (23 refs)

79-0943 Induction of Gamma-Endonuclease Sensitive Sites by Gamma-Radiation in Mammalian Cells and Their Cellular Repair are not Affected by the Presence of Thiol Compounds During Irradiation (Meeting Abstract). (Eng) van der Schans, G. P. (Medical Biological Lab. TNO, 2280 AA Rijswijk Z.H., Netherlands); Centen, H. B. *Int J Radiat Biol* 34(6): 550; 1978. (1 ref)

79-0944 The Ultrastructure of Mouse Testicular Interstitial Tissue Containing Plutonium-239 and Its Significance in Explaining the Observed Distribution of Plutonium in the Testis. (Eng) Ash, P. (MRC Radiobiology Unit, Harwell, Didcot, Oxon, England); Parker, T. *Int J Radiat Biol* 34(6): 523-536; 1978.

The distribution of plutonium-239 (²³⁹Pu) in the testis of CBA mice at various times after injection was studied by autoradiography of Araldite-embedded sections. The mice were injected in ²³⁹Pu (10 µCi/kg iv, as Pu citrate) when 12 wk old and killed 6 hr, 1 wk, 1 mo, and 3 mo later. At 6 hr, the testis contained 0.06% of the injected ²³⁹Pu; at 1-3 mo, this amount was reduced to 0.02%. At 6 hr, 38% of the ²³⁹Pu deposited in the testis was located within the seminiferous tubules, but this amount was reduced to 14% by 3 mo. At 1 wk to 3 mo, 78%-86% of the ²³⁹Pu was located within the interstitial tissue. Early in this period, ²³⁹Pu was deposited diffusely in the interstitial tissue, but by 3 mo, 47% was concentrated in the macrophages. This was a real change in distribution, since the amount of ²³⁹Pu in the testis remained constant from 1 wk to 3 mo. Electron microscopy indicated that the accumulation of ²³⁹Pu in the macrophages may occur in two ways: (1) phagocytosis of dead cells containing ²³⁹Pu; and (2) ²³⁹Pu may follow the transfer of waste products of hormone synthesis from Leydig cells into macrophages. If the second pathway proves correct, there would be a buildup of ²³⁹Pu in macrophages following injection of even small amounts, which could result in the increased irradiation of spermatogonial stem cells. (18 refs)

79-0945 Neutron Carcinogenicity in Man (Meeting Abstract). (Eng) Bond, V. P. (Brookhaven Natl. Lab., Upton, NY). *Health Phys* 35(6): 882-883; 1978. (3 refs)

79-0946 Enhancing and Inhibiting Effects of Histone Fractions on Film Sarcoma. (Eng) Lavelle, S. M. (Dept. Experimental Medicine, Univ. Coll., Galway, Ireland); MacIomhair, M. *Ir J Med Sci* 147(4): 145-150; 1978.

The effects of crude and fractionated calf thymus histone on film-induced sarcoma were examined in BALB mice. Crude histone and five fractions (2 lysine-rich, 2 slightly lysine rich, and 1 arginine-rich) were incorporated in Millipore filters that were afterward impregnated with gelatin. The filters were implanted into 20 mice for each test substance, and the animals were observed for 100 wk. The tumor yield in the model was low (2/20), but it was reproducible among three groups of controls. In the groups receiving the arginine-rich fraction and the two lysine-rich fractions, tumor yield was double that of controls (4/20 vs 2/20). The crude histone fraction and one of the slightly lysine-rich fractions (f2a) were mildly inhibitory to sarcoma induction. The other slightly lysine-rich fraction (f2b) was significantly inhibitory. Other studies on f2b fractions in several systems have suggested an effect on differentiation rather than on growth. Whether these findings have any relation to the occasional spontaneous regression of human tumors has yet to be determined. (42 refs)

- 79-0947 Thyroid Carcinoma Induced by Irradiation for Hodgkin's Disease. Report of a Case.** (Eng) Weshler, Z. (Dept. Oncology, Sharett Inst. Oncology, Hadasah Univ. Hosp., Jerusalem, Israel); Krasnokuki, D.; Peshin, Y.; Biran, S. *Acta Radiol [Oncol] (Stockh)* 17(5): 383-386; 1978.

A bilateral multifocal, mixed (papillar/follicular) adenocarcinoma of the thyroid was found in a 22-yr-old patient 16 yr after a total of 20 Gray units of radiation was applied to both sides of the neck, supraclavicular regions, and axillae for lymphocytic type Hodgkin's disease. Intermediate stages between adenoma and papillary and follicular adenocarcinoma were present. (17 refs)

- 79-0948 Breast Cancer Incidence among Atomic Bomb Survivors: Implications for Radiobiologic Risk at Low Doses.** (Eng) Land, C. E. (Environmental Epidemiology Branch, Div. Cancer Cause and Prevention, NCI, NIH, Public Health Service, U.S. Dept. Health, Education, and Welfare, Bethesda, MD, 20014); McGregor, D. H. *J Natl Cancer Inst* 62(1): 17-21; 1979.

The results of dose-response analyses of 1950-1969 breast cancer incidence data for Japanese survivors of the atomic bomb blasts in Hiroshima and Nagasaki are presented. In seeking evidence of a dose effect, a summary contingency analysis was used with a single linear contrast for increasing linear dose with av breast cancer dose. The procedure was adjusted for possible confounding between dose and age at time of blast or city of exposure and concentrated statistical power on the hypothesis that incidence increased linearly with increasing dose. It was found that the inference for a radiation effect did not depend solely on interpolation between values

of 0 and high doses. In a second analysis, a theoretical form suggested by radiobiologic principles was used to investigate the extent to which linear interpolation may overestimate or underestimate breast cancer risk at low doses. The analysis provided direct evidence of a radiation carcinogenesis effect to the breast at doses < 40 rads to breast tissue. The paucity of incidence data required simplification of the original linear form for the dose response, but the risk estimate obtained with the use of the simplified form was not greater than estimates obtained with models that fit the data more closely. (8 refs)

- 79-0949 Adenocarcinoma of the Gallbladder in Guinea Pigs.** (Eng) Hoch-Ligeti, C. (Registry Experimental Cancers, Div. Cancer Cause and Prevention, NCI, NIH, Public Health Service, U.S. Dept. Health, Education and Welfare, Bethesda, MD, 20014); Congdon, C. C.; Deringer, M. K.; Stewart, H. L. *J Natl Cancer Inst* 62(2): 381-386; 1979.

Adenocarcinoma of the gallbladder was studied in two inbred strains (2 and 13) and one noninbred stock of guinea pigs exposed to whole-body γ - or x-irradiation (8.8-0.11 R, 8 hr/day, from young adulthood to death or until a predetermined integral exposure had been given, or single doses of 310, 360, or 420 R) or left untreated for their lifespans. Tumors developed in 17/68 untreated and 26/83 irradiated animals of strains 2 and 13. Although the effect of irradiation was not dose-dependent, irradiation of inbred males increased the occurrence of gallbladder carcinoma from 19% to 30% and the number with metastases from 14% to 86%, suggesting an indirect systemic effect of irradiation. Inbred females did not show this increase. Significantly fewer (9/98) noninbred than inbred animals of either sex developed tumors after irradiation, and no gallbladder carcinomas were found in nine untreated noninbred guinea pigs. The tumors were mostly well-differentiated and located in the fundus or neck of the gallbladder. The intrahepatic bile ducts were never involved in the carcinomatous process, but they were often distended and obstructed. Direct invasion to the liver was the most common route for metastasis, as well as through lymphatic and blood vessels to lymph nodes, mesenteries, omenta, abdominal wall, liver, lungs, bones, and spleen. This is the first report of the occurrence of spontaneous gallbladder adenocarcinoma in guinea pigs. (10 refs)

See also:

- *(Rev.): 79-0612, 78-0615, 79-0616, 79-0617, 79-0618, 79-0619, 79-0620, 79-0624.
 *(Chem.): 79-0655, 79-0656, 79-0657, 79-0677, 79-0707, 79-0746, 79-0747, 79-0779, 79-0780, 79-0811, 79-0865, 79-0887, 79-0922.
 *(Viral): 79-0989.
 *(Immun.): 79-1046, 79-1057.
 *(Path.): 79-1091, 79-1099, 79-1113, 79-1114.
 *(Epid.-Biom.): 79-1146, 79-1147, 79-1148.

VIRAL CARCINOGENESIS

- 79-0950 Identification of Avian Leukemia Virus by the RIP Test.** (Rus) Zaretskaia, L. I. (All-Union Veterinary Res. Inst. Poultry Farming, Moscow, USSR); Popova, L. S.; Zelenskii, V. P. *Veterinariia* (10): 98-99; 1978.

The restricted interference phenomenon (RIP) test was used to identify avian leukemia virus (ALV). The test is based upon the strict specificity of the interference phenomenon between ALV and Rous sarcoma virus (RSV). Liver and spleen specimens obtained from chickens with a provisional diagnosis of lymphoid leukemia were analyzed by complement fixation for the presence of group-specific (GS) antigen. Cultures that contained GS antigen at a titer of 1:16-1:64 were added to primary cultures of chick embryo fibroblasts (CEF); after two passages, these cultures were infected with RSV. The CEF culture was considered to be contaminated with ALV if it was > 10 times more resistant to infection with RSV than control CEF cultures. Thirty-three variants of leukemia-sarcoma viruses were isolated among the 87 sample cultures, 12 of which were identified as ALV. Serologically, they comprised 5 A-type, 2 B-type, 2 C-type, 1 D-type, and 2 AB-type strains. (no refs)

- 79-0951 Specific RNA Sequences and Gene Products of MC29 Avian Acute Leukemia Virus.** (Eng) Mellon, P. (Dept. Molecular Biology and Virus Lab., Univ. California, Berkeley, CA, 94720); Pawson, A.; Bister, K.; Martin, G. S.; Duesberg, P. H. *Proc Natl Acad Sci USA* 75(12): 5874-5878; 1978.

The *onc* gene of the defective avian acute leukemia RNA virus MC29 was defined biochemically and compared to the *src* gene of Rous sarcoma virus (RSV). Specifically, MC29-specific sequences on the viral genome (a 28S RNA) were identified and located, and the proteins encoded by these sequences were investigated. Using ring-necked pheasant virus as a helper, MC29-specific sequences and sequences hybridized by DNA complementary to other avian tumor virus RNA's [group-specific (GS) cDNA] were defined in terms of their RNase T₁-resistant oligonucleotides and located on a map of all large T₁ oligonucleotides of viral RNA. Sixty percent of sequences were hybridized by GS cDNA, and 40% were hybridized only by MC29-specific cDNA. Oligonucleotides of GS sequences mapped between 0.0 and 0.4 and between 0.7 and 1 map unit from the 3'-poly(A) end, but oligonucleotides of MC29-specific sequences mapped between 0.4 and 0.7 map unit. Cell-free translation of MC29 RNA yielded three proteins with approx mol wts of 120,000 (P120mc), 56,000 (P56mc), and 37,000 (P37mc). P120mc, which is translated only from full-length 28S RNA, contained both MC29-specific peptides and serological determi-

nants and peptides of the conserved, internal GS antigens of avian tumor viruses. MC29 RNA contained sequences related to the GS *gag* gene, found near the 5' end, that were followed by M29-specific sequences. It is concluded that P120mc is translated from the 5' 60% of the RNA and that it includes a segment translated from the specific sequences. The transforming *onc* gene of MC29 may consist of the specific and some GS RNA sequences, and P120mc, which is also found in transformed cells, may be the *onc* gene product. (36 refs)

- 79-0952 Replication Defective, Transforming Virus of Strain R Avian Erythroblastosis Virus.** (Eng) Owada, M. (Res. Inst. Microbial Diseases, Osaka Univ., Yamada-kami, Suita, Osaka-fu 565, Japan); Kamahora, T.; Yoshida, M.; Toyoshima, K. *Gann* 69(6): 857-858; 1978.

Nonproducer (NP) cells induced by transformation of chick embryo fibroblasts (CEF) with avian erythroblastosis virus (AEV) strain R were studied. The transformed cells were highly refractile and had a slender fusiform morphology. Virus production was negative as determined by focus and reverse transcriptase assays, but transforming virus was rescued after superinfection of the NP cells with Rous-associated virus 1 (RAV-1). AEV thus rescued showed subgroup A host range, whereas the infecting AEV-R showed subgroup B host range. The morphologies induced by AEV-R and the rescued AEV-R were identical. Infectious center assay of rescued AEV and AEV-R showed reduction of focus formation to about 1/20 to 1/40 of normal. Polyacrylamide gel electrophoresis of the RNA from the rescued virus showed two major peaks, one corresponding to RAV-1 RNA and one specific for AEV. (11 refs)

- 79-0953 Selection of Methionine tRNAs by Avian Oncocornaviruses.** (Eng) Piper, P. W. (Dept. Molecular Virology, Imperial Cancer Res. Fund Labs., Lincoln's Inn Fields, London WC2A 3PX, England); Elder, K. T. *Nucleic Acids Res* 5(12): 4761-4779; 1978.

In view of the finding that the free 4S RNA of avian RNA tumor viruses is greatly enriched in one of the four methionine transfer RNA's of the host cells, tRNA-Met, the difference in the relative proportions of tRNA-Met isoacceptors in host cell, viral-free, and viral 70S-associated tRNA pools was investigated. It was assumed that the viral tRNA-Met forms are identical to the corresponding tRNA's of mouse and chick cells. Specifically, three hypotheses were analyzed: (1) the three tRNA-Met isoacceptors tRNA-Met,

tRNA-Met₃, and tRNA-Met₄ (forms 2-4) could be functionally disparate and insert methionine at different AUG codons in messenger RNA; (2) the three forms might not represent three distinct tRNA's but various conformations or modification states, separable by column chromatography, of a single nucleotide sequence; (3) form 4 could be preferentially acquired by oncornaviruses as the result of an unequal distribution of isoacceptor tRNA's within different compartments of the host cell. There was no evidence of a role for different tRNA-Met isoacceptors in the tRNA modulation of protein synthesis. Structural studies of forms 3 and 4 of mouse myeloma cells showed that these two tRNA's differ in primary structure and are not interconvertible by modification. The third hypothesis was tested by analyzing the tRNA-Met isoacceptor content of crude chick fibroblast cell fractions isolated by differential centrifugation. The results suggest that tRNA-Met species are partitioned into different cellular compartments; ie, cellular compartmentalization of tRNA's might be the major factor preventing the incorporation of significant amounts of forms 1-3 into viral-free 4S RNA. Avian myeloblastosis virus reverse transcriptase was shown to bind specifically form 4 and tRNA-Trp in whole-cell tRNA. Therefore, the free form 4 in the virion particle may exist substantially bound to virion-associated transcriptase. Although form 4 has no primer role in DNA synthesis, its association with transcriptase is possibly not fortuitous. (29 refs)

- 79-0954 Analysis of Integrated Avian RNA Tumor Virus DNA in Transformed Chicken, Duck, and Quail Fibroblasts.** (Eng) Sabran, J. L. (Dept. Microbiology, Univ. Pennsylvania, Philadelphia, PA, 19174); Hsu, T. W.; Yeater, C.; Kaji, A.; Mason, W. S.; Taylor, J. M. *J Virol* 29(1): 170-178; 1979.

The state of integration of avian sarcoma virus DNA in the genomes of transformed chicken, duck, and quail fibroblasts was deduced by restriction enzyme digestion of total cell DNA, gel electrophoresis, and subsequent analysis by the procedure of Southern using a ³²P-labeled complementary DNA probe made with viral RNA as a template. The cells used were either mass-infected cultures or clones of infected cells selected by their ability to form colonies in agar. For both mass-infected cultures and clones of cells of all three species, integration occurred at a specific site on the viral genome but appeared to occur at many sites on the cell genome. At least some of the integrated viral DNA existed as intact nonpermuted species flanked by direct terminal repeats of least 0.134 megadalton (217 base pairs). For each of 12 transformed quail clones studied, it was possible to detect, after digestion with *Kpn*I, unique junctions between viral and cellular DNA. That is, at the level of analysis used in this study, the integration site on the cell genome for each clone was different. However, within each of the 17 chicken and 9 duck clones of transformed cells, a heterogeneity presumably occurred during the outgrowth of the cell clone popula-

tion, in that identifiable cell-virus junction fragments could not be detected readily. (24 refs)

- 79-0955 Isolation of a Sarcoma Virus from a Spontaneous Chicken Tumor.** (Eng) Itohara, S. (Veterinary Pathology, Faculty Agriculture, Yamaguchi Univ., Yoshida, Yamaguchi 753, Japan); Hirata, K.; Inoue, M.; Hatsuoka, M.; Sato, A. *Gann* 69(6): 825-830; 1978.

A sarcoma virus isolated from a spontaneous tumor of a White Leghorn hen was characterized. The tumor had the characteristics of a fibro- or myxofibrosarcoma and was maintained by transplantation in chicks over a period of several years. Cell-free extract from the tumor produced tumors at the site of inoculation after sc injection into 3-wk-old chicks. Type-C virus-like particles were observed in the extracellular spaces and vacuoles of the tumor cells. Inoculation with the original viral stock produced pocks on 10-day-old embryos and induced transformation of chick and quail embryo fibroblasts. The virus was designated Yamaguchi 73 sarcoma virus (Y73). The virus showed the host range and interference patterns of subgroup A with a possible minor subgroup E component. Cloned virus had the same envelope characteristics as uncloned virus. The replicating capacity of Y73 suggested that it was defective, and this was supported by the infectious center assay. The defectiveness could not be defined. (19 refs)

- 79-0956 Proviruses of Avian Sarcoma Virus Are Terminally Redundant, Co-extensive with Unintegrated Linear DNA and Integrated at Many Sites.** (Eng) Hughes, S. H. (Dept Microbiology, Univ. California, San Francisco, CA, 94143); Shank, P. R.; Spector, D. H.; Kung, H. J.; Bishop, J. M.; Varmus, H. E.; Vogt, P. K.; Breitman, M. L. *Cell* 15(4): 1397-1410; 1978.

The DNA from 15 clones of avian sarcoma virus (ASV)-transformed normal rat kidney cells was analyzed with restriction endonucleases and molecular hybridization techniques to determine the location and structure of proviral DNA. Each of the 20 complete or incomplete proviruses studied appeared to be located in a different site in cellular DNA, and at least 10 were located in regions separated by more than 10⁷ daltons. Two of the original 15 clones contained proviral DNA located at two distinct sites in the host cell DNA. These proviruses appeared to be identical to the single proviruses observed in six other clones. Seven clones contained at least one unit of abnormal viral DNA integrated into the host genome. Three of the four anomalous proviruses analyzed were deletion mutants lacking 25%-65% of the genetic content of ASV; the fourth was normal but for a novel site for cleavage by *Eco*RI. Both ends of at least 18 proviruses contained sequences specific to both the 3' and 5' termini of viral RNA. The organization of these terminally redundant sequences appeared identical to that of the 300 base pair re-

peats previously found at the ends of unintegrated linear DNA. Thus, proviral DNA is coextensive, or nearly coextensive, with unintegrated linear DNA and has a structure denoted as CELL DNA-3'5'-----3'5'-CELL DNA. (48 refs)

79-0957 Characterization of a Normal Avian Cell Protein Related to the Avian Sarcoma Virus Transforming Gene Product. (Eng) Collett, M. S. (Dept. Pathology, Univ. Colorado Medical Center, Denver, CO, 80262); Brugge, J. S.; Erikson, R. L. *Cell* 15(4): 1363-1369; 1978.

A normal avian cell protein antigenically related to the pp60src viral protein responsible for transformation by avian sarcoma virus (ASV) was identified by immunoprecipitation of uninfected chicken, duck, quail, and pheasant cells with serum from marmosets bearing ASV-induced tumors. In each avian species tested, the normal cell protein was a 60,000-daltons phosphoprotein (pp60) that was not related to any of the ASV structural proteins. However, preadsorption of the antiserum with cell extracts containing pp60src prevented immunoprecipitation of pp60. The chymotryptic peptides generated by partial proteolysis of pp60 and pp60src were very similar, except that one of the major peptides of pp60 showed an altered mobility. The phosphopeptide maps of pp60src and pp60 differed completely. Regardless of cellular growth conditions, the level of pp60 was approx thirty- to fiftyfold lower than that of pp60src in ASV-infected cells. The normal cell protein appeared to be functionally dissimilar to pp60src in that it lacked detectable protein kinase activity. (20 refs)

79-0958 Mapping Unintegrated Avian Sarcoma Virus DNA: Termini of Linear DNA Bear 300 Nucleotides Present Once or Twice in Two Species of Circular DNA. (Eng) Shank, P. R. (Dept. Microbiology, Univ. California, San Francisco, CA, 94143); Hughes, S. H.; Kung, H. J.; Majors, J. E.; Quintrell, N.; Guntaka, R. V.; Bishop, J. M.; Varmus, H. E. *Cell* 15(4): 1383-1395; 1978.

Physical maps of the DNA's of several strains of avian sarcoma virus (ASV) were constructed. On infection of permissive quail cells with ASV, a linear DNA was synthesized in the cytoplasm and three major species of viral DNA were synthesized in the nucleus: a form indistinguishable from the linear cytoplasmic species; closed circular DNA; and proviral DNA inserted covalently into the genome of the host cell. The linear DNA appeared to be a structure with a large (approx 300 base) natural repeat at both termini (eg, 3'5'-----3'5'). Two closed circular species of approx monomeric size were identified. The less abundant species contained all the sequences identified in the linear DNA, including two copies in tandem of the 300 nucleotide 3'5' repeat. The major species lacked about 300 base pairs mapped to the region of the repeated sequence. Thus it presumably contains only a single copy of that sequence. (50 refs)

79-0959 An Avian Oncovirus Mutant (SE 21Q1b) Deficient in Genomic RNA: Biological and Biochemical Characterization. (Eng) Linial, M. (Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104); Medeiros, E.; Hayward, W. S. *Cell* 15(4): 1371-1381; 1978.

The isolation and characterization of a coordinately defective (cd) mutant of Rous sarcoma virus (RSV) that is deficient in packaging of genomic RNA is reported. The RSV-transformed quail cells that shed the mutant virus (SE 21Q1b) contained all three functional messenger RNA (mRNA) classes in approx the same amounts present in wild-type virus-infected cells. In addition, the mutant virus was not deficient in any of the four known viral gene products, *gag*, *env*, *pol*, or *src*. However, less than 1% of the RNA in the virus particles released from the quail cells was virus-specific, and no functional 39S genomic RNA could be detected in the SE 21Q1b virions. Instead, the virions contained primarily a heterogeneous population of cellular RNA's. These results and data from superinfection experiments suggest that transcription and translation of viral RNA are normal in 21Q1b cells, but that some defect in the 21Q1b integrated genome prevents efficient packaging of the 39S RNA into virions. The nature of the defect may be complex and involve both genome structure and virus-coded factor(s). (34 refs)

79-0960 Metabolism of Acetylcholine Receptor in Chick Embryo Muscle Cells: Effects of RSV and PMA. (Eng) Miskin, R. (Lab. Chemical Biology, Rockefeller Univ., New York, NY, 10021); Easton, T. G.; Maelicke, A.; Reich, E. *Cell* 15(4): 1287-1300; 1978.

The effects of phorbol myristate acetate (PMA) and transformation by a temperature-sensitive mutant of Rous sarcoma virus (RSV) on the steady-state concentration, synthesis, and degradation of the nicotinic acetylcholine receptor (AChR) in chick embryo muscle cells were studied. In normal muscle cell cultures, the synthesis and degradation rates of AChR decreased systematically with the age of the cultures, and the rates could be manipulated by changes in the composition of the culture medium. Transformation by RSV increased the rate of AChR degradation, leading to a reduction in the surface receptor concentration. PMA also increased the rate of receptor degradation and decreased the rate of synthesis, greatly reducing the steady-state level of surface AChR. The muscle cell system allows quantitative measurement of an integral membrane protein and its metabolism, and it may serve as a more general model for studies of transformation-associated alterations in membrane and surface receptor metabolism. (36 refs)

79-0961 Lactate Dehydrogenase Isozymes in Rous Sarcoma and Muscle Tissue of Tumor-bearing Chickens. (Rus) Parina, E. V. (State Univ., Kharkov, USSR);

Mikhailova, S. A.; Antonov, V. S. *Ukr Biokhim Zh* 50(6): 706-710; 1978.

The distribution of various lactate dehydrogenase (LDH) isozymes was studied in 40-day-old chicks and adult hens infected with Rous sarcoma virus (0.2 ml of tumor suspension, im). On days 6, 10, and 14 after infection, the birds were sacrificed, and tumor and muscle tissue specimens were subjected to electrophoresis in polyacrylamide gels. In the chicks, changes in the isozyme spectrum of the tumor could be detected on day 14 (increased level of LDH5 and decreased levels of LDH1 and LDH2); in the adult hens, similar changes could be detected on day 6. Development of the Rous sarcoma affected the LDH spectrum in the intact (contralateral) muscle: the adult hens showed a decrease in LDH1 and LDH2 levels on days 10 and 14, compared with day 6 in the chicks. (7 refs)

79-0962 In Vitro Synthesis of Infectious Transforming DNA by the Avian Sarcoma Virus Reverse Transcriptase. (Eng) Clayman, C. H. (Dept. Microbiology, Univ. Minnesota Medical Sch., Minneapolis, MN, 55455); Mosharrafa, E.; Faras, A. J. *J Virol* 29(1): 242-249; 1979.

Infectious DNA molecules capable of transforming chicken embryo fibroblasts can be synthesized by Rous sarcoma virus (RSV)-associated reverse transcriptase in vitro under reaction conditions that facilitate a max yield of genome length DNA transcripts (approx 7.5-10 kilobases). Analysis of the DNA product synthesized by detergent-disrupted RSV under these conditions indicates that DNA complementary to viral RNA (minus-strand DNA) is genome length in size, whereas DNA complementary to genome length minus-strand DNA (plus-strand DNA) appears as subgenomic-length molecules that are 300-3,500 nucleotides long. These features of the DNA product synthesized by RSV reverse transcriptase in vitro are similar to those identified in the cytoplasm of cells shortly after infection and lend credence to studies of the mechanism of reverse transcription in vitro and their significance to proviral DNA synthesis in vivo. (31 refs)

79-0963 Integration of Rous-associated Virus Type 0 Provirus in Susceptible Chicken Cells. (Eng) Hefti, E. (Dept. Pathology, Univ. Chicago, Chicago, IL, 60637); Baluda, M. A. *J Virol* 29(1): 409-412; 1979.

This study was made to determine whether the concentration of endogenous proviral sequences per cell remains constant after in vitro cell culture and whether additional Rous-associated virus type 0 (RAV-0) proviruses can integrate after superinfection of susceptible cells. The number of viral genome equivalents per haploid cell genome was determined in normal chicken embryos from three selected chicken lines and in cultured fibroblasts (CEF) from these embryos. The cellular concentration of endogenous proviral DNA was

similar in embryos from chickens of lines SPAFAS, 7, 15, 7 x 15, and 100. The concentration of proviral DNA was not affected by in vitro cultivation in CEF from lines that do not spontaneously produce virus nor in CEF from line 7, which lacks receptors for RAV-0. There was, however, a restricted increase in the number of integrated proviral genome equivalents in CEF from line 7 x 15, which produces RAV-0 and can support replication of this virus, and in CEF from line 15 experimentally infected with RAV-0. Thus, additional RAV-0 proviral sequences can be integrated in cells with appropriate surface receptors, ie, of a phenotype other than C/E, but in nonproducing or C/E cells, the proviral DNA concentration remains constant during in vitro culture. (18 refs)

79-0964 Extracellular Cleavage of the Glycoprotein Precursor of Rous Sarcoma Virus. (Eng) Klemenz, R. (Swiss Inst. Experimental Cancer Res., 1066 Epalinges, Switzerland); Diggelmann, H. *J Virol* 29(1): 285-292; 1978.

The kinetics of the cleavage of pr92gp, the high-mol-wt precursor of the two glycoproteins (gp85 and gp35) of Rous sarcoma virus, were followed to determine the site of cleavage. The viral glycoproteins were detected by immunoprecipitation with anti-gp85 and anti-gp35 serum. Pulse-chase experiments showed that little or no intracellular cleavage of the precursor took place during the time in which most of the newly synthesized viral glycoprotein was exported from the cells. Soon after its synthesis, however, pr92gp underwent some modification that made it migrate slightly faster on sodium dodecyl sulfate-polyacrylamide gels. Under steady-state conditions, the precursor was the predominant form of intracellular viral glycoprotein. Virus that was harvested every 2 min from infected cells prelabeled for 90 min with ³H-mannose contained mostly uncleaved and only a little mature glycoprotein. By incubation of this freshly released virus in serum-free buffer, the majority of the glycoprotein precursor could be cleaved into mature gp85 and gp35. Virus harvested every 10 min contained only mature glycoproteins. Thus, almost all cleavage of the glycoprotein precursor takes place extracellularly, in newly budded virus particles. (35 refs)

79-0965 Recombination Between Viral and Cellular Sequences Generates Transforming Sarcoma Virus. (Eng) Wang, L. H. (Rockefeller Univ., New York, NY, 10021); Halpern, C. C.; Nadel, M.; Hanafusa, H. *Proc Natl Acad Sci USA* 75(12): 5812-5816; 1978.

The genomic RNA sequences of recovered avian sarcoma viruses (rASV's), their parental transformation-defective (td) viruses, and the Schmidt-Ruppin strain of Rous sarcoma virus subgroup A (SR-A) were characterized and compared by oligonucleotide (ON) fingerprinting. Special emphasis was placed on their *src*-specific sequences. Of six sarcoma-specific

ON's present in SR-A RNA, three to six were missing in the RNA's of the four td mutants examined. All six isolates of rASV had regained these six ON's. In addition, most rASV RNA's had three new ON's not present in the RNA of the td mutants or of SR-A. The newly obtained ON's were located between 800 and 2,600 nucleotides from the 3' end of rASV RNA, a region that corresponds to the *src* region of SR-A RNA mapped previously. Furthermore, the viral RNA's of two td mutants isolated from a clone of rASV lacked most *src*-specific ON's, including the three new ones. There were no differences among the RNA's of td, SR-A, and rASV in the regions outside of *src*. Thus, RNA sequences that rASV's have acquired from cells in the process of conversion from a td to a transforming virus are mapped within the *src* region and segregate with the transforming function. Some of the sequences are new and some are identical with those in SR-A RNA. The results strongly suggest that rASV's have been generated by recombination between td viral and cellular *src* sequences that have been identified in normal chicken and other avian cells. It is possible that different ASV's may have a common (cellular) origin for their *src* genes. (26 refs)

79-0966 Relationship Between Phase of Mitotic Cycle of Human Embryo Cells and Transformation with

Rous Sarcoma Virus and Polyoma Virus. (Rus) Karazhas, N. V. (Dept. Tumor Etiology and Diagnosis, Inst. Epidemiology and Microbiology, Moscow, USSR); Shevliagin, V. I. *Tsitologiya* 20(12): 1413-1418; 1978.

The susceptibility of human embryo cells during different phases of mitosis to transformation with Rous sarcoma virus (RSV) and polyoma virus (PV) was evaluated. Synchronized cell suspensions were contaminated with RSV or PV together with Sendai virus. The mitotic cycle of the human fibroblasts lasted 18 hr. Of five cultures infected with RSV during the S phase, four showed transformation 2-3 wk after infection (compared with 2/5 cultures infected during G₂ and 0/5 infected during G₁). Of seven cultures infected with PV during S, two showed transformation 2-3 wk after contamination (compared with 0/7 cultures infected during G₂ or G₁). (11 refs)

79-0967 Changes in Rous and Polyoma Viruses During Their Synthesis in the Cells of Unnatural Hosts.

(Rus) Karazhas, N. V. (Lab. Virus Etiology Tumors, N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR); Bykovskii, A. F.; Cherepantseva, E. A.; Chizhevskaya, V. I.; Shevliagin, V. I. *Biull Eksp Biol Med* 86(12): 710-713; 1978.

An attempt was made to overcome intraspecies virus specificity and to evaluate the possibility of the synthesis of oncogenic viruses in heterologous cells. The morphological and karyological properties of human embryo-derived continuous cell lines transformed by Rous sarcoma virus (RSV)

(line 23) or by polyoma virus (line P-2) were analyzed. The presence of RSV in cells of line 23 was shown by complement fixation reaction, immunofluorescence assay, and electron-microscopic examination. RSV cultivated in the human embryo cells retained the ability to transform chick embryo cells (natural host), but showed increased affinity for mammalian tissues. Similar results were obtained for polyoma virus cultivated in P-2 cells. (11 refs)

79-0968 Differential Mortality and Lesion Responses to Reticuloendotheliosis Virus Infection in

Marek's Disease-resistant and Susceptible Chicken Lines. (Eng) Scofield, V. L. (Hopkins Marine Station, Stanford Univ., Pacific Grove, CA, 93950); Spence, J. L.; Briles, W. E.; Bose, H. R. *Immunogenetics* 7(2): 169-172; 1978.

The mortality patterns and lesion responses of line N (Marek's disease-resistant) and line P (Marek's disease-susceptible) chickens infected with reticuloendotheliosis virus (REV) were compared to investigate the possibility of genetic control of tumorigenesis in the REV system. Chickens of line N (B-locus genotype *B¹/B¹*) and line P (*B⁰/B⁰*) were hatched on the same day and inoculated ip with REV (5 x 10³ plaque-forming units) at age 3.5 wk. Five of nine line N chickens died 12-16 days after infection with prominent hepatosplenomegaly. Eight of the 10 line P chickens died, 3 within 20 days of infection (all negative for visceral lesions) and the others 24-44 days after infection. Visceral lesions were present at death in 2/8 line P chickens. Thus, line N and P chickens respond differently to tumorigenesis by REV on the basis of lesion incidence and mortality patterns. From these results and those of previous studies, it is concluded that the overall resistance to tumorigenesis by the several oncogenic viruses in chickens is polygenic and controlled by loci within and outside of the major histocompatibility complex. (21 refs)

79-0969 Enhanced Oncornavirus Expression in Marek's Disease Tumors from Specific-Pathogen-Free

Chickens. (Eng) Campbell, W. F. (Dept. Microbiology, Mayo Clinic, Rochester, MN, 55901); Frankel, J. W. *J Natl Cancer Inst* 62(2): 323-328; 1979.

The recovery of an oncornavirus from cell cultures derived from kidney tumors induced in 4-day-old SPAFAS chickens by intraabdominal inoculation with 100 focus-forming units of Marek's disease herpesvirus (MDHV) is described. MDHV-inoculated chickens demonstrated increasing levels of infectious avian leukosis virus (ALV) RNA in kidney, ovary, and spleen tumors compared with control kidney, liver, and spleen tissue. DNA from these cultured kidney tumor cells annealed to an ALV complementary DNA probe at the same rate and exhibited the same extent of homology as DNA from cultured kidney cells, indicating the absence of exogenous ALV proviral sequences. Radioimmunoassay indicated that, like the vertically transmitted endogenous ALV of sub-

group E, these oncornaviruslike particles replicated in permissive turkey embryo fibroblast (TEF) culture, but not in nonpermissive chicken embryo fibroblast (CEF) culture of the C/E phenotype. These oncornavirus particles served as a helper virus to form Rous sarcoma virus pseudotypes, which produced foci in TEF cultures but not in C/E CEF cultures. The expression of endogenous or exogenous oncornaviruses should not be excluded as a contributory factor in the development of Marek's disease, Burkitt's lymphoma, or other human neoplasms with which herpesviruses have been associated. (46 refs)

- 79-0970 Avian Oncovirus Mill Hill No. 2: Pathogenicity in Chickens.** (Eng) Alexander, R. W. (Diagnostic Electron Microscopy Lab., Veterans Admin. Hosp., Gainesville, FL, 32602); Moscovici, C.; Vogt, P. K. *J Natl Cancer Inst* 62(2): 359-366; 1979.

The transforming and oncogenic effects of Mill Hill No. 2 (MH2), an avian C-type oncovirus, were studied by intraabdominal, iv, and sc injection into chickens of phenotypes C/E, C/CE, and Q/BC, and resulting tumors were studied by light and electron microscopy. MH2 induced leukemias and soft-tissue sarcomas, but the most striking pathogenic effect of this virus was production of carcinomas in the liver and kidney. The iv route was the most effective, giving rise to a higher percentage of birds with liver and kidney carcinoma, sometimes as early as 1 wk after injection. For example, of 50 C/E chickens inoculated iv with 2×10^3 focus-forming units, there were 28 hepatomas, 20 nephroblastomas, 6 lymphomas, and 3 sarcomas. A subgroup A MH2 pseudotype with Rous-associated virus type 3 as helper [MH2 (RAV-3)] induced substantial numbers of solid tumors, and, unlike standard MH2, also produced a high incidence of an acute unclassified leukemia. Helper viruses naturally associated with MH2 (MH2AV) produced only lymphomas, at a low incidence. The soft-tissue sarcomas produced at the injection site were composed of undifferentiated round cells, and a definite tissue of origin could not be determined. In the kidney, adenocarcinoma-like tumors with a malignant stroma were present. Hepatocarcinomas were the dominant tumors found in the liver. The undifferentiated lymphomas produced by MH2AV were composed of round cells and were highly malignant. These studies showed that MH2 has high oncogenic potential. The tumors induced by MH2 and myelocytomatosis virus MC29 are compared. (33 refs)

- 79-0971 The N-Terminal Sequence of Three Coat Proteins of Foot-and-Mouth Disease Virus.** (Eng) Strohmaier, K. (Bundesforschungsanstalt für Viruskrankheiten der Tiere, Tübingen, W. Germany); Wittmann-Liebold, B.; Geissler, A. W. *Biochem Biophys Res Commun* 85(4): 1640-1645; 1978.

The N-terminal sections of the sequences of the three coat

proteins VPgly, VPasp, and VPthr of foot and mouth disease virus (FMDV) were determined and compared with the first 10 amino acids of the corresponding Mengo virus proteins. In the proteins of the two viruses beginning with aspartic acid, 5/10 amino acids were found to be in identical positions. This suggests that the VPasp-proteins of both viruses are related. (17 refs)

- 79-0972 Properties of Morphologically Variant Haploid Frog Cells Formed by Combined Treatment with Mengo Virus and the Polyene Antibiotic Mediocidin.** (Eng) Fisher, P. B. (Wistar Inst. Anatomy and Biology, Philadelphia, PA, 19104); Goldstein, N. I.; Bryson, V. *In Vitro* 14(12): 961-965; 1978.

ICR 2A cells (haploid frog cells), ICR 2A M cells (3 cloned populations of ICR 2A cells resistant to 5 μ g/ml of the polyene antibiotic mediocidin), and ICR 2A M/MV cells (5 cloned populations of morphologically variant haploid frog cells produced by exposure of ICR 2A cells to mediocidin and Mengo virus) were compared with respect to surface glycoproteins, concanavalin A (Con A) agglutinability, and growth properties in liquid media. The ICR 2A M/MV cells contained an apparently high-mol-wt surface glycoprotein not found in ICR 2A or ICR 2A M cells and exhibited a higher degree of agglutinability in Con A, a higher plating efficiency, and a shorter population doubling time at 23 C than did ICR 2A or ICR 2A M cells. α -Methyl glucoside and α -methyl mannoside prevented the Con A agglutination of all cell lines. The differences exhibited between ICR 2A M/MV cells and the parental cells suggest that alterations resembling transformation had occurred in the former as a result of combined treatment with mediocidin and Mengo virus. (16 refs)

- 79-0973 Differential Expression of Poly (A)-adjacent Sequences of Mammary Tumor Virus RNA in Murine Mammary Cells.** (Eng) Dudley, J. P. (Dept. Microbiology, Univ California Sch. Medicine, San Francisco, CA, 94143); Rosen, J. M.; Butel, J. S. *Proc Natl Acad Sci USA* 75(12): 5797-5801; 1978.

Two complementary DNA (cDNA) probes were used to study mouse mammary tumor virus (MMTV) gene expression in several BALB/c mammary tumor cell lines, in normal lactating BALB/c tissue, and in a cloned C3H tumor cell line. cDNA primed by random calf thymus DNA oligodeoxynucleotides was representative of the entire MMTV genome, but cDNA primed by (dT)12-18 had a decreased genetic complexity and hybridized predominantly with poly(A)-adjacent sequences at the 3' end of MMTV RNA. These probes were characterized with respect to rates of hybridization with template RNA, size (as determined by alkaline sucrose gradient centrifugation), and thermal stability of the cDNA-MMTV RNA hybrids. The ability of these probes to protect

¹²⁵I-labeled MMTV RNA or ¹²⁵I-labeled poly(A)-adjacent MMTV RNA sequences from S₁ nuclease digestion was also determined. Hybridization studies indicated that there were approx 20 times more oligo(dT)-primed sequences in BALB/c lactating glands than there were sequences representing the entire genome, but in BALB/c tumor cells the ratio of oligo(dT)-primed to calf thymus-primed cDNA sequences was reduced to approx 4:1. In virus producer C3H tumor cells, there was only a twofold excess of oligo(dT)-primed sequences over that detected with a representative cDNA. These results are consistent with the existence of subgenomic viral messenger RNA (mRNA) species, integration of partial proviral copies, or differential mRNA processing in virus nonproducer and producer cells. (27 refs)

79-0974 Large-Scale Production of Mouse Mammary Tumor Virus in the Absence of Endogenous Murine Leukemia Virus. (Eng) Benton, C. V. (Viral Oncology Program, NCI, Frederick Cancer Res. Center, Frederick, MD, 21501); Harshman, J. S.; Robinson, O. R.; Shibley, G. P. *Appl Environ Microbiol* 37(1): 148-158; 1979.

The large-scale production and purification of mouse mammary tumor virus (MMTV) in the absence of detectable endogenous murine leukemia virus (MuLV) is reported. Mm5mt/c₁ (Mm5) cells, which were established from a C3H mouse adenocarcinoma, were used. Frozen Mm5 cultures of the same passage were cultured using a scale-up scheme, and dexamethasone was incorporated into the growth medium at the final passage. Max virus expression was observed by the third or fourth harvest, coincident with monolayer confluency. Harvests were stored at 4 C and then pooled prior to virus purification in 38% sucrose and 34% sucrose. A 1,000-fold concentration of MMTV particles and an approx 16,000-fold reduction in total protein were thereby achieved. Expression of endogenous Mm5 MuLV was increased by completely dispersing the Mm5 cells into single cell suspensions and by constantly agitating the suspensions before seeding. The cells were then stressed by rapid passage at low split ratios and elevated temperature. A three-step sucrose gradient was used to separate MMTV particles, which banded at densities from 1.17 to 1.21 g/cm³, from MuLV particles, which banded at densities from 1.13 to 1.17 g/cm³. Competition radioimmunoassay was the most sensitive method for detecting and quantitating MuLV in MMTV preparations. Over 25,000 liters of MMTV-containing Mm5 fluids have been produced from 22 production runs, and after purification and concentration, >225 product lots have been found to be free of detectable MuLV while containing high levels of MMTV. (30 refs)

79-0975 Rigid Plasma-Membrane-derived Vesicles, Enriched in Tumour-associated Surface Antigens (MLr), Occurring in the Ascites Fluid of a Murine Leukemia (GRSL). (Eng) van Blitterswijk, W. J. (Div. Cell Biolo-

gy, Antoni Van Leeuwenhoek-Huis, Netherlands Cancer Inst., Amsterdam, The Netherlands); Emmelot, P.; Hilkmann, H. A.; Hilgers, J.; Feltkamp, C. A. *Int J Cancer* 23(1): 62-70; 1979.

The extracellular membranes (ECM) of thymus-derived spontaneous murine (GR/A strain) leukemia (GRSL) cells were purified and compared with plasma membranes isolated from a GRSL cell homogenate. The protein-phospholipid ratio and the specific sialic acid, 5'-nucleotidase, and mammary tumor virus-induced antigens (MLr) levels were markedly higher in the ECM than in the plasma membranes. The ECM also showed a 3-fold increase in the cholesterol-phospholipid molar ratio and a 10-fold increase in sphingomyelin content compared with the plasma membranes. It appeared that the extracellular material contained only random cell debris very shortly after inoculation of GRSL cells into syngeneic mice. With time, however, ECM survived or arose anew and showed a higher lipid microviscosity than either the subcellular fractions or purified plasma membranes obtained from whole cells. The data indicate that ECM are clearly derived from the cell surface of living cells. (38 refs)

79-0976 Tryptic Peptide Analysis of gag Gene Proteins of Endogenous Mouse Type C Viruses. (Eng) Albino, A. (Sloan-Kettering Inst., New York, NY, 10021); Korngold, L.; Mellors, R. C. *J Virol* 29(1): 102-113; 1979.

The internal viral proteins of known endogenous mouse C-type viruses were analyzed and compared with the use of tryptic peptide mapping. Tryptic digests of the internal proteins p30, p15, p12, and p10 of mouse xenotropic, ecotropic, and amphotropic C-type viruses were subjected to cation-exchange chromatography. Analysis of these maps revealed that the p30 proteins from representative isolates of all three viral subgroups were distinguishable. The p15 proteins were all unique. The p12 proteins of NZB xenotropic and wild-mouse amphotropic viruses were not identical and yielded peptide maps remarkably different from that of the ecotropic virus. The p10 proteins of xenotropic and ecotropic viruses were identical and were dissimilar to that of the wild-mouse amphotropic virus. The results further delineate the interrelatedness and polymorphism of these gag gene proteins. (40 refs)

79-0977 Wild Mouse RNA Tumor Viruses: A Nongenetically Transmitted Virus Group Closely Related to Exogenous Leukemia Viruses of Laboratory Mouse Strains. (Eng) Barbacid, M. (Lab. Cellular and Molecular Biology, NCI, Bethesda, MD, 20014); Robbins, K. C.; Aaronson, S. A. *J Exp Med* 149(1): 254-266; 1978.

Prototype wild mouse C-type tumor viruses were characterized with respect to their genetic relationship to the mouse

cell and to known exogenous and endogenous viruses of laboratory mouse strains. Amphotropic viruses isolated from wild mice trapped in separate geographical areas were found to be biochemically and immunologically indistinguishable, whereas amphotropic and ecotropic viruses naturally infecting the same animal were found to be *env* gene variants. Molecular hybridization studies demonstrated that neither host range variant was endogenous to the *Mus musculus* genome, although each demonstrated partial nucleotide sequence homology. Wild mouse C-type viruses exhibited much closer molecular and antigenic relatedness to the exogenous virus subgroup (Friend, Moloney, and Rauscher murine leukemia virus) than to prototype endogenous viruses isolated from laboratory mice. The evidence indicates that exogenous mouse C-type viruses have been maintained in nature over a long period of evolution as a separate virus group, causative of tumors in mice by a mechanism solely involving their transmission as infectious agents. (48 refs)

- 79-0978 Spontaneous Expression of Murine Endogenous Viruses in Hamster x Mouse Hybrid Cells.** (Eng) Park, S. S. (NCI-VA Medical Oncology Branch, NCI and Veterans Admin. Hosp., Washington, DC, 20422); Gazdar, A. F.; Lalley, P. A.; Minna, J. D.; Francke, U. *Int J Cancer* 23(1): 52-61; 1979.

The spontaneous expression patterns of murine leukemia virus (MuLV) from mouse spleen cultures and hamster x mouse spleen hybrid cells were compared. The hybrid cells preferentially segregated mouse chromosomes but retained a complete set of hamster chromosomes. None of 13 BALB/c spleen cultures expressed virus, whereas 6/20 hybrid clones expressed N-tropic or N- and X-tropic viruses. All AKR cultures and 5/7 hybrids expressed N-tropic but not X-tropic virus. All 6 NZB cultures and 5/8 hybrids expressed X-tropic virus, but virus expression did not occur in NIH Swiss or NIH Swiss/nude spleen or hybrid cultures. Mouse chromosome 7 was required, but not sufficient, for the initial expression of N-tropic virus; chromosome 2 may be necessary and sufficient for X-tropic virus release. The results indicate that spontaneous expression of MuLV strains does not require the followup MuLV-related genes: *Fv-1* (chromosome 4), *Fv-2* (chromosome 9), *Rec-1* (replication of ecotropic virus, chromosome 5), and *GV-1* and *H-2* (chromosome 17). (27 refs)

- 79-0979 Complexity and Abundance of Murine Leukemia Virus-related Nuclear and Messenger RNA Sequences in Mouse Embryo Cell Lines Which Are Differentially Sensitive to Carcinogen-induced Virus Activation.** (Eng) Getz, M. J. (Dept. Pathology and Anatomy, Mayo Clinic and Mayo Foundation, Rochester, MN, 55901); Elder, P. K.; Moses, H. L. *Cancer Res* 39(2, Part 1): 321-327; 1979.

The abundance and sequence complexity of endogenous murine leukemia virus (MuLV)-related nuclear and messenger RNA (nRNA and mRNA) sequences were determined in non-virus-producing AKR-2B cells derived from high-leukemia-incidence mice; in AKR-MCA cells, a chemically transformed virus-producing derivative; and in C3H/10T1/2 cells, derived from low-tumor-incidence mice. The polyribosome-associated, EDTA-released mRNA from AKR-2B cells contained MuLV-related sequences of lower complexity (as measured by hybridization with complementary DNA) than those found in the nucleus of the same cells. These MuLV-related sequences appeared to be of lower mol wt than the nuclear sequences and to contain only about 50% or less of the MuLV genomic complexity. In contrast, the steady-state nRNA isolated from both AKR-2B and AKR-MCA cells as well as the mRNA from AKR-MCA cells represented 100% of the MuLV genomic complexity, although the MuLV-related sequences in AKR-MCA mRNA were of lower mol wt than the AKR-MCA nRNA, sequences. The C3H/10T1/2 cells contained polysomal RNA and nRNA MuLV-related sequences of similar complexity (46% and 34%, respectively, of the total viral genome), revealing no posttranscriptional regulation at this level. Moreover, the hybridization assay revealed that the viral-specific RNA sequences in AKR and C3H cells shared a high degree of sequence homology. Although the complexity of the MuLV-related nRNA sequences was equivalent in AKR-2B and AKR-MCA cells, the relative abundance of the sequences was much greater in the AKR-MCA cells. The differences in the apparent complexity, abundance, and subcellular distribution of MuLV-related RNA sequences are consistent with the hypothesis that C3H cells maintain a more stringent control over the expression of endogenous MuLV-related genes than do AKR cells. The data also indicate that the nucleotide sequence complexity of endogenous C-type, viral-specific mRNA and nRNA can be regulated independently. (29 refs)

- 79-0980 Congenital Transmission of Murine Leukemia Virus from Wild Mice Prone to the Development of Lymphoma and Paralysis.** (Eng) Gardner, M. B. (Dept. Pathology, Univ. Southern California, Sch. Medicine, 2025 Zonal Ave., Los Angeles, CA, 90033); Chiri, A.; Dougherty, M. F.; Casagrande, J.; Estes, J. D. *J Natl Cancer Inst* 62(1): 63-70; 1979.

Experiments show that maternal congenital transmission of infectious murine leukemia virus, primarily via milk, is the major route of virus spread in Lake Casitas (LC) wild mice and in crosses of LC mice with uninfected wild and laboratory mice. An indirect extrachromosomal male transmission in utero of LC virus also readily occurred in matings of viremic LC males with C57L females, but apparently not with other uninfected wild or NIH Swiss females. Both amphotropic and ecotropic classes of LC murine leukemia viruses were potentially transmissible by congenital and venereal epigenetic means and could induce the same two diseases, lymphoma

and paralysis, that occur naturally in LC wild mice. Lymphoma and paralysis failed to occur in uninfected LC mice or in their hybrid progeny that escaped congenital infection. (48 refs)

79-0981 C-Type Virus Particles in Human Urogenital Tumours After Heterotransplantation into Nude Mice. (Eng) Wunderli, H. (Div. Urology, Dept. Surgery, Duke Univ. Medical Center, Durham, NC, 27710); Mickey, D. D.; Paulson, D. F. *Br J Cancer* 39(1): 35-42; 1979.

C-type virus particles formed in heterotransplants of 5/14 human urogenital tumors that had been serially transferred in NIH(S) nude mice were studied ultrastructurally. In most cases, the particles were found exclusively within the supporting connective tissue of the tumors. Peroxidase labeling with antimouse serum indicated that this connective tissue was of mouse origin. In one transitional-cell bladder carcinoma, C-type particles were detected in the connective tissue, the interspace between epithelial cells, and vacuoles between epithelial cells. Numerous particles were observed budding from epithelial cell membranes. Competition radioimmunoassays showed the presence of murine leukemia virus interspecies p30 antigen in extracts of the transplanted human tumors and in two spontaneous mouse tumors. No p30 antigens were found in tissues of mice that had not been used for heterotransplantation. The data suggest that endogenous nude mice viruses were activated by the human tumor grafts and that they subsequently infected the human tumor cells and formed particles. (24 refs)

79-0982 Redistribution and Modulation of Gross Murine Leukemia Virus Antigens Induced by Specific Antibodies. (Eng) Joachim, H. L. (Dept. Pathology, Lenox Hill Hosp., 100 E. 77th St., New York, NY, 10021); Sabbath, M. *J Natl Cancer Inst* 62(1): 169-180; 1979.

The modulation of Gross murine leukemia virus (G-MuLV)-induced rat leukemia cells (culture LT₁, from a leukemic thymus) by rat anti-G-MuLV antibodies was analyzed in vitro. Rat anti-G-MuLV antisera were added to the leukemia cell cultures for variable periods of time, and the redistribution of virus particles and membrane virus antigens was determined by electron microscopy, indirect immunofluorescence, and immunoelectron microscopy. LT₁ cells grown in medium with the antisera were generally larger, with more basophilic cytoplasm and large, regularly shaped nuclei that frequently had the appearance of immunoblasts. The cytoplasm occasionally included tubular structures, filaments, and multivesicular bodies. Virus particles and membrane virus antigens were redistributed in the form of polar patches and caps, and budding and detachment of virus particles were no longer seen. Substantial decreases in cytotoxicity indexes accompanied these changes. Cytotoxicity tests revealed an increased resistance to cytolysis when

fresh, nonheated rat serum was added to the heat-inactivated anti-G-MuLV rat serum. A heat-labile serum factor was apparently required for the in vitro promotion of cellular antigen modulation. This modulation paralleled similar changes obtained in vivo by transplantation of leukemia cells in rats with high anti-G-MuLV antibody titers. The importance of antigen modulation in this system concerns its direct relationship with the malignant potential of the leukemia cells. (37 refs)

79-0983 Gross Murine Leukemia Virus-induced Alterations in the Thymus of Preleukemic AKR Mice. (Eng) Beardsley, T. R. (Lab Nuclear Medicine and Radiation Biology, Warren Hall, Univ. California, Los Angeles, 900 Veteran Ave., Los Angeles, CA, 90024); Hays, E. F. *Cancer Res* 39(2, Part 1): 480-486; 1979.

Thymic morphology and thymocyte and T-cell function were studied in AKR mice to separate age-related structural and functional changes in the thymus from those caused by Gross murine leukemia virus (GMuLV). Newborn mice were inoculated ip at 3 days of age with either 0.1 ml of a 0.9% NaCl solution (AKR-N) or 0.1 ml cell-free filtrate containing GMuLV (AKR-V) and studied in the 5th wk of life. Both thymic wt and total thymic cell count were significantly decreased in AKR-V mice. The response of AKR-V thymocytes to both phytohemagglutinin (PHG) and alloantigen in mixed lymphocyte culture was significantly increased over that of normal thymic cells, as was graft-vs-host reactivity. Conversely, response to concanavalin A (Con A) was significantly decreased in the AKR-V thymocytes. Treatment with cortisone generally increased the reactivity of both groups of mice to PHG and Con A, and their responsiveness in the graft-vs-host reaction, accentuating the relationships already mentioned. Although AKR-V lymph node cells had a significantly higher background of thymidine uptake, the responses of T-cells from spleen and lymph nodes in all of these tests were otherwise generally similar. Reduction in the number of cortical cells responsive to Con A is suspected as the cause of thymic wt loss, while the relative increase in reactive cells caused by this cortical cell reduction may account for the increased reactivity to PHG and alloantigen in the thymus. (26 refs)

79-0984 Inhibitory Effect of Growth Hormone on Gross Passage A Virus-induced Thymus Leukemia in C3Hf Mice. (Eng) Duquesnoy, R. J. (Dept. Microbiology, Medical Coll. Wisconsin, Milwaukee, WI, 53201); Pedersen, G. M. *Cancer Res* 39(2, Part 1): 415-418; 1979.

The effect of growth hormone (GH) on Gross passage A (GPA) virus-induced leukemia was studied in C3Hf mice inoculated with ovine GH (potency, 0.86 IU/mg) starting the first week after birth (100 µg/day in week 1, 100 µg 3x/wk in weeks 2 and 3, 100 µg 2x/wk in weeks 4 and 5, and 100

$\mu\text{g/wk}$ until the age of 3 mo). Control mice received bovine serum albumin (BSA) injections or no injections at all. Half of the mice from all three groups received 0.2-ml sc injections of a 1:20 dilution of GPA virus extract on day 4 of life. The GPA virus-infected mice experienced a high incidence of lymphoid leukemia with a minimum latent period of 3 mo. The median survival time (MST) of the female mice was 225, 135, and 108 days, respectively, in the GPA-GH, GPA-BSA, and GPA-only groups; the MST of the male mice was 297, 178, and 162 days, respectively. Because the GPA-infected mice also developed salivary gland tumors in large numbers but noninfected controls did not, it was suspected that the GPA extract contained another tumor-inducing agent. The GPA-GH group exhibited a high mortality from salivary gland tumors after 7 mo of age, so that the enhancement of survival by GH might have been more significant than that observed. In the GPA-GH, GPA-BSA, and GPA-only groups, the leukemia mortality rate was 35%, 74%, and 80%, in females and 45%, 75%, and 89%, in males, respectively. Thus, GH treatment produced a significant reduction in mortality compared with the other two groups. All three groups of male GPA-infected mice and the GPA-BSA and GPA-only groups of female mice died predominantly with type A leukemia, whereas 50% of the GPA-GH female mice that died with leukemia had type-B tumors. Therefore, GH treatment of female mice can alter the nature of induced leukemias as well as delay their development. The results indicate that GPA virus-induced leukemia can be classified on the basis of thymus involvement (ie, type A with T-cell leukemia or type B with thymus-independent leukemia). (31 refs)

79-0985 Isolation and Characterization of a Tumor Cell Surface Antigen from Spontaneously Transformed BALB/c Mouse Fibroblasts. (Eng) Kamm, A. R. (Dept. Biochemistry, Coll. Medicine, Univ. Arizona, Tucson, AZ, 85724); Grimes, W. J. *Proc Natl Acad Sci USA* 75(12): 5912-5916; 1978.

The detection, isolation, and partial characterization of a cell-surface antigen on three cultured fibroblast cell lines derived from BALB/c mice are described. The antigen migrates as a polypeptide of approx 100,000 daltons in a discontinuous sodium dodecylsulfate-polyacrylamide gel electrophoresis system, can be labeled by metabolic incorporation of ^3H -glucosamine or by the ^{125}I /lactoperoxidase method, and can be isolated by concanavalin A affinity chromatography. It was shown to be antigenic in BALB/c mice, it is present on immunogenic transformants, and it appears to be correlated with the rejection of immunogenic tumor cells. This antigen also shares antigenic determinants with Moloney leukemia virus (MLV), as MLV-specific antiserum precipitated the 100,000-dalton protein from viral and immunogenic spontaneous transformants. This virus-related antigen comigrated with the major iodinated cell-surface protein of these transformants. Sera taken from mice bearing immunogenic tumors contained cell-surface-directed antibodies against the

tumor cells. Rabbit antiserum to the purified antigen demonstrated a marked preference for the surfaces of immunogenic tumor cells vs normal cells or nonimmunogenic tumor cells. (24 refs)

79-0986 The Effect of pH on the Infectivity and Production of Murine Retroviruses. (Eng) Walker, J. R. (Dept. Biological Sciences, Univ. Warwick, Coventry CV4 7AL, England); Avery, R. J. *FEMS Microbiology Letters* 5(1): 47-51; 1979.

Experiments demonstrating that the infectivity, production, and reverse transcriptase activity of murine sarcoma/leukemia virus are decreased by zwitterionic buffers at pH levels other than 7.4 are presented. The effect of pH at different temperatures was also studied. (8 refs)

79-0987 Phenotypically Distinct Target Cells for Murine Sarcoma Virus and Murine Leukemia Virus Marrow Transformation In Vitro. (Eng) Greenberger, J. S. (Joint Center Radiation Therapy, Dept. Radiation Therapy, Harvard Medical Sch., Boston, MA, 02115). *J Natl Cancer Inst* 62(2): 337-348; 1979.

The effects of isolates of Harvey, Moloney, and Kirsten murine sarcoma virus (H-, M-, and Ki-MuSV, respectively) on long-term cultures of NIH Swiss mouse bone marrow were determined, and the results were compared with those of the associated C-type helper virus alone. (Rauscher murine leukemia virus, R-MuLV, or Balb:virus-1). An in vitro hematopoietic microenvironment was established from explanted fragments of bone marrow with the use of corticosteroid-reconstituted horse serum. Infection with Ki-MuSV plus either helper virus coat reduced granulopoiesis and produced neoplastic transformation of macrophages and preadipocytes in the adherent cell population within 4-wk. Ki-MuSV-transformed, virus-releasing macrophages formed clusters of 4-49 cells in methylcellulose-containing medium in the absence of colony-stimulating factor (CSF), synthesized lysozyme, esterase-M, and CSF, and produced tumors on inoculation iv into adult NIH Swiss mice or ip into newborn NIH Swiss mice at 10^6 cells/mouse. Addition of H-MuSV or M-MuSV pseudotypes with R-MuLV helper virus also transformed macrophages and preadipocytes in the adherent cell population and decreased granulopoiesis. The induced macrophage cell lines were morphologically and histochemically indistinguishable from those induced by Ki-MuSV. In contrast, the helper viruses accelerated the proliferation of atypical granulocytes in the cultures. Over a 9-wk period, there were increasing numbers of atypical myeloblasts and promyelocytes that showed dyssynchronous nuclear-cytoplasmic maturation, basophilic granulation, cytoplasmic vacuolation, and formation of incompletely maturing CSF-dependent granulocyte-macrophage colonies in vitro and small spleen colonies in vivo. These data indicate

that there are phenotypically distinct biologic target cells for transformation by MuSV and MuLV in mouse marrow culture. (46 refs)

79-0988 "sarc" Sequence Transcription in Moloney Sarcoma Virus-transformed Nonproducer Cell Lines. (Eng) Bondurant, M. (St. Jude Children's Res. Hosp., Memphis, TN, 38101); Ramabhadran, R.; Green, M.; Wold, W. S. *J Virol* 29(1): 76-82; 1979.

³H-Labeled complementary DNA(sarc) that is complementary to the murine sarcoma virus (MSV)-specific portion of the Moloney MSV (M-MSV) genome was prepared and used as a hybridization probe to (1) analyze transcription of M-MSV-specific sequences and (2) determine the relative copy number of these sequences in the DNA of several M-MSV-transformed nonproducer cell lines derived from NIH 3T3 cells. M-MSV-specific RNA was quantitated in the cytoplasm of the three clonal NIH 3T3 cell lines 71 N CL 5, 71 N CL 6, and 71 N CL 3. By the criteria of cell morphology and agglutination by concanavalin A, CL 5 cells are highly transformed, CL 6 cells are almost normal in the sense that they resemble the parent NIH 3T3 cells, and CL 3 cells are phenotypically intermediate. The amounts of cytoplasmic MSV-specific RNA correlated well with the relative degrees of transformation of the cell lines, varying > 35-fold between the least transformed (CL 6) and most transformed (CL 5) lines. Superinfection of CL 5 or CL 6 with Moloney murine leukemia virus resulted in a fivefold increase in MSV-specific RNA in the cell cytoplasm. Evidence from ³H-labeled complementary DNA:cell DNA hybridization studies indicated that the quantity of M-MSV-specific RNA in the nonproducer lines was not directly related to DNA provirus copy number in the cell DNA. Although CL 5 and CL 6 differ greatly in transformation characteristics and in MSV-specific RNA content, they each apparently contain about two copies of MSV-specific DNA sequence per haploid genome. Thus, factors such as site of provirus integration may be of primary importance in determining virus-specific transcription and cell transformation. (30 refs)

79-0989 Radiation Induction of Endogenous Type C Virus from Mouse Cells Transformed In Vitro by Murine Sarcoma Virus. (Eng) Niwa, O. (Dept. Experimental Radiology, Faculty Medicine, Kyoto Univ., Sakyo-ku, Kyoto 606, Japan); Sugahara, T. *J Natl Cancer Inst* 62(2): 329-335; 1979.

Cell lines from AKR and BALB/c mouse embryos were compared for their sensitivity to x-ray induction of endogenous C-type virus. No virus activity was detected in AKR 2B cells or a secondary culture of AKR mouse embryo fibroblasts after 500 or 1,000 R of x-irradiation. In contrast, K-Balb cells, a Balb/3T3 cell line nonproductively transformed by Kirsten murine sarcoma virus, were sensitive to x-irradiation.

The number of cells with induced virus increased significantly at a dose as low as 50 R, which exerted almost no effect on cell survival. The induction frequency increased with increasing dose of x-rays up to 400 R. Only Balb:virus-2 was activated by x-irradiation, whereas both Balb:virus-1 and Balb:virus-2 were activated after treatment of K-Balb cells with 5-iodo-2'-deoxyuridine. UV light and 4-nitroquinoline 1-oxide (4-NQO) also induced virus expression in K-Balb cells. X-rays, UV light, and 4-NQO gave almost identical virus-induction frequencies of 3×10^{-4} . The virus-induction frequency for 5-bromo-2'-deoxyuridine was the highest, 9.4×10^{-2} . These results indicate that the molecular mechanisms for virus induction by halogenated pyrimidines and physical and chemical carcinogens may be different and that the damages responsible for virus activation by x-irradiation may be different from lethal damages. (37 refs)

79-0990 Isolation and Characterization of a Feline Sarcoma Virus-coded Precursor Polypeptide. (Eng) Khan, A. S. (Viral Oncology Program, Frederick Cancer Res. Center, Frederick, MD, 21501); Deobagkar, D. N.; Stephenson, J. R. *J Biol Chem* 253(24): 8894-8901; 1978.

A feline sarcoma virus (FeSV)-coded precursor polypeptide was isolated and characterized. FeSV pseudotype virions produced by superinfection of nonproductively transformed mink and rat cells efficiently incorporated the 130,000-mol-wt precursor polypeptide (FeSV Pr130) and several of its intermediate cleavage products, including a 25,000-mol-wt product containing feline leukemia virus (FeLV) p12 and p15 and a protein of 70,000 mol wt. FeSV Pr130 was highly acidic (pI 3.9) and was reactive in competition immunoassays for two FeLV gag gene-coded structural proteins (p15 and p12); it failed to compete for other FeLV-coded structural proteins or viral-coded reverse transcriptase. ¹²⁵I-labeled FeSV Pr130 was precipitated by high-titered goat serum against FeLV p15, p12, and, to a lesser extent, p30. Naturally immune cat serum with known high-titered antibody against the transformation-specific feline oncornavirus-associated cell membrane antigen (FOCMA) also precipitated Pr130 efficiently, even after extensive absorption with FeLV. The data indicate that Pr130 contains a nonstructural component corresponding to the 60,000-mol-wt FeSV-coded, FOCMA cross-reactive protein expressed in FeSV-transformed mink cells. A highly specific competition immunoassay for the structural component of FeSV Pr130 is described. (34 refs)

79-0991 Inhibition of Human Lymphocyte Mitogen and Antigen Response by a 15,000-Dalton Protein from Feline Leukemia Virus. (Eng) Hebebrand, L. C. (Dept. Veterinary Pathobiology, Ohio State Univ., Columbus, OH, 43210); Olsen, R. G.; Mathes, L. E.; Nichols, W. S. *Cancer Res* 38(2, Part 1): 443-447; 1979.

The immunosuppressive effects of a 15,000-dalton protein (p15) from a C-type feline leukemia virus (FeLV) on the peripheral blood lymphocyte (PBL) response of normal human subjects to several mitogens and antigens were studied by a lymphocyte blast transformation test. The PBL responses of 4/6 subjects were suppressed 70%-96% when the cells were exposed to 10.0 μg /well concanavalin A (Con A) in the presence of 5.0 μg of p15. Likewise, the response to 1.2 μg /well phytohemagglutinin was only 12%-40% that of control values in 3/5 subjects. The three subjects who responded to streptokinase-streptodornase (108 units/well) and 2/3 who responded to *Candida albicans* (0.05 ml/well) were suppressed 68%-91% when their PBL were cultured with 5.0 μg of p15. Immunosuppressive doses of 2.0 and 5.0 μg /well of p15 appeared to have no cytotoxic effect on the cultures, as no cell counts dropped below the original well count. The number of cap-forming lymphocytes induced by Con A decreased 51%-91% in the presence of 5.0 μg p15, as indicated by lymphocyte membrane studies with fluorescein isothiocyanate-Con A. Thus, a C-type virion protein can induce immunological dysfunction in vitro. (11 refs)

- 79-0992 Biochemical and Immunological Characterization of a Reverse Transcriptase from Human Melanoma Tissue.** (Eng) Chandra, P. (Gustav-Embsen-Zentrum der Biologischen Chemie, Abteilung für Molekularbiologie, Klinikum der J. W. Goethe-Universität, Theodor-Stern-Kai 7, D-6 Frankfurt 70, W. Germany); Balıkcıoglu, S.; Mildner, B. *Cancer Lett* 5(6): 299-310; 1978.

The reverse transcriptase (RT; RNA-directed DNA polymerase) from human melanoma tissue was purified and characterized biochemically and immunologically. Purification was accomplished by serial centrifugation of the filtered tissue homogenate to isolate the microsomal fraction of the cells, solubilization of this fraction, and then successive diethylaminoethyl cellulose (DE-23 and DE-52) and phosphocellulose column chromatography. The purified enzyme (mol wt 68,000) was most efficient in transcribing the synthetic primer templates (dG)₁₈(rC)n and (dG)₁₈(rC)n, followed by (dT)₁₂(rA)n. It also transcribed a 70S RNA from Rauscher leukemia virus, but it failed to transcribe (dT)₁₀(dA)n, indicating that the enzyme is free of DNA polymerase- β activity. Failure to utilize (dA)₁₂ and (dG)₁₈ as initiators showed that the RT did not contain any terminal deoxynucleotidyl transferase activity. The enzyme had a pH optimum of 8.0, an Mn²⁺ optimum of 0.6 mM, and a KCl optimum of 60 mM. Serological studies indicated that the RT was not antigenically related to DNA polymerases from simian sarcoma virus, avian myeloblastosis virus, Rauscher leukemia virus, and human myelofibrotic spleen. However, the human melanoma enzyme showed close antigenic similarity to the DNA polymerases from baboon endogenous virus and rhabdomyosarcoma virus RD-114, the endogenous virus of the cat. (19 refs)

- 79-0993 Infectivity Tests of Secretions and Excretions From Cattle Infected with Bovine Leukemia Virus.** (Eng) Miller, J. M. (U.S. Dept. Agriculture, Science and Education Admin., Federal Res., Natl. Animal Disease Center, P.O. Box 70, Ames, IO, 50010); Van Der Maaten, M. J. *J Natl Cancer Inst* 62(2): 425-428; 1979.

Secretions and excretions from cattle (Holstein-Friesian, Angus, Guernsey, and Simmental) with persistent bovine leukemia virus (BLV) infections were analyzed for BLV in a sheep bioassay to determine their relative importance as sources of virus for transmission in contact situations. Test sheep of a mixed breed were injected with the fluids, and infection was confirmed by development of antibody to the BLV glycoprotein antigen (detected by the agar gel immunodiffusion) and reisolation of virus from sheep peripheral blood WBC. The virus was detected in milk from 4/6 cows examined, one of which was from a commercial dairy. Likewise, the colostrum of 1/4 cows produced persistent positive results of virus infection in one test sheep. None of the sheep inoculated with semen from eight bulls or with nasal secretions, urine, or saliva from two cows developed BLV-precipitating antibodies. The presence of BLV in colostrum and milk indicates these materials may be potential sources of infection for nursing calves. Moreover, the presence of BLV infectivity in milk from a commercial dairy cow raises questions regarding the possible significance of this virus as a hazard to human health. (26 refs)

- 79-0994 Postnatal and Prenatal Transmission of the Bovine Leukemia Virus under Natural Conditions.** (Eng) Piper, C. E. (Hazleton Labs. America, Inc., 9200 Leesburg Turnpike, Vienna, VA, 22180); Ferrer, F. J.; Abt, D. A.; Marshak, R. R. *J Natl Cancer Inst* 62(1): 165-168; 1979.

The distribution of bovine leukemia virus (BLV) and BLV antibodies was studied in a well-characterized multiple-case leukemia herd (BF) of purebred Jersey cattle by the syncytia infectivity and virus neutralization antibody assays, respectively. Of 84 calves examined before their colostrum meal, only 15 were positive for BLV and/or BLV antibody. All 52 calves examined after colostrum ingestion and before age 5 mo had acquired maternal antibodies to BLV, but only 12 (all infected at birth) were positive for infectious BLV. These antibodies were transient, with only 15 animals (13 originally infected) being positive for antibody at 7-10. The incidence of BLV infection did not change significantly during the first 10 mo of life. In keeping with standard husbandry practices, calves were separated from the adult herd after weaning and kept apart up to 14-16 mo of age. Therefore, the rapid increase in BLV infection rate (93% of cases by age 24 mo) beginning at age 12-16 mo was assumed to result from contact with the exposed herd. Of 17 BLV calves born antibody-negative and raised in isolation to age 24 mo after being weaned from their BLV-infected dams, only 3 became BLV-positive, vs 17/17 animals in a control group that joined the herd at the normal time. These results indicate (1) that

prenatal transmission of BLV is infrequent; (2) that during the first weeks of life, calves are protected by milk-borne maternal antibodies from contact or milk-borne BLV infection; and (3) that BLV infection persists despite the presence of actively produced or passively acquired BLV-neutralizing antibodies. (18 refs)

79-0995 Noncondylomatous Wart Virus Infection of the Postmenopausal Cervix. (Eng) Laverty, C. R. (Dept. Pathology, King George V Hosp., Camperdown, New South Wales 2050, Australia); Booth, N.; Hills, E.; Cossart, Y.; Wills, E. J. *Pathology* 10(4): 373-378; 1978.

Noncondylomatous papilloma (wart) virus infection of the cervix is more common than heretofore realized. Although most of the patients are young, two cases in postmenopausal women were found, one with cytological evidence of persistence of the lesion for 12 yr. The two cases show that warty atypia must be considered in the interpretation of cytological atypia in postmenopausal women. (7 refs)

79-0996 Translation of Polyoma Virus T Antigens In Vitro. (Eng) Hunter, T. (Tumor Virology Lab., Salk Inst., San Diego, CA, 92112); Hutchinson, M. A.; Eckhart, W. *Proc Natl Acad Sci USA* 75(12): 5917-5921; 1978.

The in vitro translation of polyoma virus-specific RNA isolated from the cytoplasm of infected mouse 3T6 cells during the late stage of infection produced three tumor (T) antigens with mol wts of approx 90,000 (90K), 60K, and 22K. The tryptic peptide patterns of these antigens were very similar or identical to the patterns of the corresponding proteins in polyoma-infected cells. Their ability to incorporate methionine from initiator transfer RNA in vitro showed that the NH₂ termini of all three primary translation products are retained in the mature molecules; ie, the antigens share common NH₂-terminal sequences. Polyoma complementary RNA (cRNA) coded for a protein that was slightly larger than but otherwise similar to the 22K T antigen, but it did not produce the 90K or 60K protein, which suggests that the generation of messenger RNA's (mRNA's) for these T antigens requires the removal of intervening sequences. The mRNA coding for the 90K T antigen was approx 280 nucleotides smaller than the RNA's coding for the 60K and 22K T antigens. The 60K T antigen may be translated partially in a different reading frame from sequences also coding for the 90 K T antigen. The demonstration that polyoma virus codes for three different T antigens with different functions and cellular locations raises the possibility that all three proteins play a role in cell transformation. (30 refs)

79-0997 Three Species of Polyoma Virus Tumor Antigens Share Common Peptides Probably near the

Amino Termini of the Proteins. (Eng) Smart, J. E. (Cold Spring Harbor Lab., P.O. Box 100, Cold Spring Harbor, NY, 11524); Ito, Y. *Cell* 15(4): 1427-1437; 1978.

The tryptic peptides of the three major tumor (T)-related proteins (100K, 55K, and 22K) from polyoma virus-infected mouse cells were studied following metabolic labeling with ³H-leucine, ³⁵S-methionine, and ³H-proline. The results indicated that there are at least five peptides that are shared by the three proteins, and that they are coded for by the region between 74 and 80 map units on the viral genome. Three peptides are shared by the 55K and 22K proteins, but not by the 100K protein; these peptides are probably derived from the region of the viral genome lying between about 80 and 85 map units. Three peptides were found only in the 22K protein; six were found only in the 55K protein; and sixteen were found only in the 100K protein. The genetic information for the unrelated peptides of the 100K and 55K proteins probably comes from the portion of the messenger RNA codes for the carboxy terminal portions of these molecules. These portions of the two proteins must differ considerably. The peptides unique to the 22K protein have also been tentatively assigned to the carboxy terminal region of the molecule. (24 refs)

79-0998 Polyoma Infected Cells Contain at Least Three Spliced Late RNAs. (Eng) Horowitz, M. (Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel); Bratosin, S.; Aloni, Y. *Nucleic Acids Res* 5(12): 4663-4675; 1978.

Poly(A)-containing polyoma cytoplasmic RNA hybridized to linear double-stranded polyoma DNA by displacing the part of the DNA strand identical to this RNA, and RNA displacement loops (R loops) were formed. Electron microscope examination of these structures showed that at least three late polyoma-specific RNA's were present and that the leader sequences at the 5' ends of these viral RNA's were not coded immediately adjacent to the bodies of the RNA's. The three RNA species may correspond to the 19S, 18S, and 16S viral messenger RNA's. Measurements of the R loops determined the locations of the bodies and leaders of the RNA's on the physical map of polyoma DNA, along with the length of the bodies, leaders, and corresponding intervening DNA sequences. (22 refs)

79-0999 Differential In Vitro Growth Properties of Cells Transformed by DNA and RNA Tumor Viruses. (Eng) O'Neill, F. J. (Dept. Microbiology, Univ. Utah, Salt Lake City, UT, 84132). *Exp Cell Res* 117(2): 393-401; 1978.

The in vitro growth properties of untransformed (UT) and RNA and DNA virus-transformed Syrian hamster, rat, and mouse cells were compared. Cells transformed by the DNA tumor viruses [simian virus 40 (SV40), adenovirus type 7 (Ad 7), and polyoma virus] grew to concentration densities that

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were markedly higher than those of UT cells or cells transformed by RNA tumor viruses (Kirsten or Moloney strains of murine sarcoma virus). However, the RNA virus-transformed cells grew to densities greater than those of UT cells. In most cases, SV40- and Ad7-transformed cells seemed smaller than UT or RNA virus-transformed cells, but the size differences, although significant, were not great enough to account for the apparent growth differences. As growing cultures of UT cells neared saturation density, the fraction of cells synthesizing DNA was minimal. The RNA virus-transformed cells were also contact-inhibited, but at a significantly higher density. In contrast, the DNA virus-transformed cells propagated to still greater densities and continued DNA synthesis at a high rate, even at very high densities. Thus, DNA virus-transformed cells are not contact-inhibited. Apparently, the ability of these cells to propagate to relatively higher densities is a reflection of an increased capacity to synthesize DNA at high densities. There were no consistent differences between the two transformed cell groups in ability to form colonies in agar, although 4/8 RNA virus-transformed lines produced colonies inefficiently or not at all. The observed differential growth properties might be applied to cultured human tumor cells. (32 refs)

79-1000 Origin of DNA Replication in Papovavirus Chromatin is Recognized by Endogenous Endonuclease. (Eng) Waldeck, W. (Institut für Virusforschung, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany); Fohring, B.; Chowdhury, K.; Gruss, P.; Sauer, G. *Proc Natl Acad Sci USA* 75(12): 5964-5968; 1978.

Evidence is given that up to 30% of the covalently closed circular DNA of simian virus 40 (SV40) and polyoma virus is cleaved in vitro to full-length linear rods by an endonuclease endogenous to isolated viral chromatin. The precise nature of this endonuclease is not known. It is not only bound to chromatin but also appears in free form in nuclear extracts. The cleavage takes place in viral chromatin either at or closely adjacent to the respective origins of DNA replication (\pm 75 base pairs). The positions of the cleavage sites were determined by aligning the different lengths of the cleavage products obtained after digestion with single-cut restriction endonucleases on the physical maps such that they started at the respective cleavage sites of the endonucleases. The full-length linear DNA rods whose ends map adjacent to the origin of DNA replication could also be isolated by sodium dodecyl sulfate/phenol extraction from both SV40-infected permissive cells and purified SV40 virions. Biological properties such as initiation of transcriptional activity may account for the structural specificity of the papovavirus chromatin in the region of the genome close to the initiation site of DNA replication. (32 refs)

79-1001 Synthesis of High Molecular Weight Antigen T of Virus SV40 in Paired Cell-free System of

Transcription-Translation. (Rus) Shtrauss, M. (Central Inst. Molecular Biology, Berlin, E. Germany); Emel'ianov, V. V.; Kalinin, V. N.; Shernek, Z.; Geissler, E.; Tikhonenko, T. I. *Vopr Virusol* (6): 669-673; 1978.

An attempt was made to synthesize tumor antigen (T antigen) in the paired cell-free transcription-translation system from *Escherichia coli* Q13 using DNA of virus SV40 as a template. Saturation of the system was observed at a DNA concentration of 6 $\mu\text{g}/\text{nl}$ (2×10^{-9} M): the yield of the protein (measured by the rate of ^{14}C -amino acid incorporation) was similar to that synthesized in the presence of a fivefold amount of plasmid ColEI DNA. Along with the relatively "short" T-antigen polypeptides, fragments with mol wt of 74 and 86 kilodaltons were found in the system, indicative of the complete expression of gene A. (23 refs)

79-1002 Surface Glycopeptide Change Triggered by Contact Between Normal Cells from Rat Liver and Their Simian Virus 40-Transformed Cells from the Same Virus. (Eng) Yokota, M. (Dept. Biological Products, Inst. Medical Science, Univ. Tokyo, P.O. Takanawa, Tokyo 108, Japan); Kato, I.; Onodera, K.; Kadosaka, T.; Aoi, Y. *J Natl Cancer Inst* 62(2): 305-312; 1979.

Surface glycopeptide (SGp) changes induced by mixed culture of normal and simian virus 40-transformed rat liver epithelial cells (WIRL-3 and SV40-WIRL-3) were investigated, along with the biologic responses of the two lines to SGp's derived from each line independently and from the mixed culture. SGp from the mixed culture showed, upon electrophoresis, a quantitative increase and a qualitative change in structure that was not detected in the SGp of normal and transformed cells cultured separately. These changes were ascribable mainly to normal cells responding to transformed cells, and a SGp change in WIRL-3 cells induced a qualitative SGp change in the SV40-WIRL-3 cells. Inhibition of ^3H -thymidine uptake of the cells by the three SGp preparations (each, 200 $\mu\text{g}/\text{ml}$ culture medium) was assessed to determine the activity of the Gp's in altering the function of the SV40-WIRL-3 cells. WIRL-3 cells were inhibited to essentially the same extent (30%) by all three Gp's, whereas SV40-WIRL-3 cells were inhibited 65% by the mixed-culture SGp, 50% by the WIRL-3 SGp, and 35% by its own SGp. From these results, it is hypothesized that the normal cell may have the ability to recognize, react with, and exert certain effects on transformed cells, with the glycocalyx playing a key role in this process. (14 refs)

79-1003 DNAs of Simian Virus 40 and Polyoma Direct the Synthesis of Viral Tumor Antigens and Capsid Proteins in Xenopus Oocytes. (Eng) Rungger, D. (Dept. Animal Biology, Univ. Geneva, CH 1224 Chene-Bourgeries, Geneva, Switzerland); Turler, H. *Proc Natl Acad Sci USA* 75(12): 6073-6077; 1978.

Experiments demonstrating that *Xenopus* oocytes transcribe and translate most or all of the genetic information contained in the simian virus 40 (SV40) genome are presented. SV40 large and small tumor antigens synthesized in the oocytes were indistinguishable, by both gel electrophoresis and ^{35}S -methionine-labeled tryptic peptide mapping, from the corresponding polypeptides synthesized in CV-1 African green monkey cells. The synthesis of large SV40 tumor antigen implies the correct splicing of its messenger RNA, which is complementary to nonadjacent nucleotide sequences in the early region of the viral genome. Polyoma DNA directed the synthesis of two polyoma tumor antigen polypeptides (57,000 M_r and small tumor antigen) and of the main capsid protein. (41 refs)

79-1004 Structure of Simian Virus 40 Chromosomes in Nuclei from Infected Monkey Cells. (Eng) Shelton, E. R. (Dept. Biological Chemistry, Harvard Medical Sch., Boston, MA, 02115); Wassarman, P. M.; DePamphilis, M. L. *J Mol Biol* 125(4): 491-514; 1978.

To avoid the appearance of potential artifacts in the study of the arrangement of nucleosomes in simian virus 40 (SV40) chromosomes, the isolation of SV40 chromosomes was avoided, and identical digestion conditions were maintained by incubating nuclei isolated from virus-infected CV-1 cells with micrococcal nuclease. This allowed a direct comparison between the structure of viral chromosomes and those of the host. To distinguish viral from cellular DNA fragments after electrophoresis in agarose gels, a previously described blotting-hybridization method was used. Cellular DNA was identified either by the same technique or by simply staining with ethidium bromide. While as many as 18 cellular DNA bands were detected in agarose gels, no more than 6 viral DNA bands were observed, and the viral DNA bands appeared broader and less well-resolved than the corresponding DNA bands from CV-1 chromatin. The av repeat distance between DNA oligomers from SV40 nucleosomes, 187 ± 11 base-pairs, was essentially the same as that observed for its host, 182 ± 6 base-pairs. These observations were independent of the extent of digestion and of the time after infection when nuclei were isolated. Since micrococcal nuclease digestion of SV40 chromosomes, both isolated and remaining in the nuclei, gave essentially the same results, the isolated chromosomes were not altered during their preparation. The results of these experiments, together with previously reported data, were used to construct a model for the arrangement of an av of 22 nucleosomes per genome in SV40 chromosomes that includes regions of nonnucleosomal DNA between some or all of the nucleosomes. (48 refs)

79-1005 Tandem Integration of Complete and Defective SV40 Genomes in Mouse-Human Somatic Cell Hybrids. (Eng) Campo, M. S. (Dept. Zoology, Univ. Edin-

burgh, Edinburgh EH9 3JT, Scotland); Cameron, I. R.; Rogers, M. E. *Cell* 15(4): 1411-1426; 1978.

The arrangement of simian virus 40 (SV40) DNA sequences integrated into human chromosome 7 was studied in two clones (Cl 10 and Cl 21) derived from mouse-human somatic cell hybrids: Cl 10 contained only one human chromosome 7 per cell, but Cl 21 contained an av of three. In the two clones, the integration site differed in both the host and the viral DNA. In Cl 10, the viral integration site lay close to position 0.37 in the early region of the SV40 genome; in Cl 21 DNA, it lay around position 0.7 to 0.8 in the late region of the viral genome. There was only one integration site in each clone. However, the viral DNA was integrated in more than one chromosome 7 in Cl 21 cells, the integration site being the same in all copies of chromosome 7 in these cells. In clone Cl 10, the integrated viral DNA had a complex arrangement of 6 tandem repetitions of complete and defective viral genomes. In clone Cl 21, there were 18 tandem repetitions of the viral genome. It is concluded that human chromosome 7 contains at least two different sites that can support the integration of SV40 DNA. (39 refs)

79-1006 Association of Simian Virus 40 T Antigen with Simian Virus 40 Nucleoprotein Complexes. (Eng) Mann, K. (Dept. Biology, Univ. Alaska, Anchorage, AK, 99504); Hunter, T. *J Virol* 29(1): 232-241; 1979.

The simian virus 40 (SV40) replicative intermediate (RI) DNA- or SV40 mature supercoiled (I) DNA-containing nucleoprotein (NP) complexes were examined for the presence of both the 100,000-dalton (100K) and 17K SV40 tumor (T) antigens. Viral NP complexes were extracted from the nuclei of SV40-infected TC7 cells by low-salt treatment in the absence of detergent, followed by sedimentation on neutral sucrose gradients. Two forms of SV40 NP complexes, those containing SV40 (RI) DNA and those containing SV40 (I) DNA, were separated from one another and were found to have sedimentation values of 125S and 93S, respectively. ^{35}S -methionine-labeled proteins in the NP complexes were analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. In addition to VP1, VP3, and histones, a protein with a mol wt of 100K was present in the NP complexes containing SV40 (I) DNA. The 100K protein was confirmed as SV40 100K T antigen, both by immunoprecipitation with SV40 anti-T serum and by tryptic peptide mapping. The 100K T antigen was predominantly associated with the SV40 (I) DNA-containing complexes. The 17K T antigen, however, was not associated with the SV40 (I) or (RI) DNA-containing NP complexes. The functional significance of the SV40 100K T antigen in the SV40 (I) DNA-containing NP complexes was examined by immunoprecipitation of complexes from ts458-infected TC7 cells. The 100K T antigen was present in NP complexes extracted from cells grown at the permissive temperature but was clearly absent from complexes extracted from cells grown at the nonpermissive temperature and shifted up to the nonpermissive temperature for 1

hr before extraction, suggesting that the association of the 100K T antigen with the SV40 NP complexes is involved in the initiation of SV40 DNA synthesis. (43 refs)

- 79-1007 Relationship Between T-Antigen and Tumor-specific Transplantation Antigen in Simian Virus 40-transformed Cells.** (Eng) Chang, C. (NCI, NIH, Bethesda, MD, 20014); Martin, R. G.; Livingston, D. M.; Luborsky, S. W.; Hu, C. P.; Mora, P. T. *J Virol* 29(1): 69-75; 1979.

Simian virus 40 (SV40) tumor (T) antigen and tumor-specific transplantation antigen (TSTA) were partially purified from the nuclei of SV AL/N cells, an SV40-transformed mouse embryo fibroblast line, by precipitation with ammonium sulfate and chromatography on diethylaminoethyl- and DNA-cellulose and studied to clarify their relationship. T antigen was assayed by complement fixation and TSTA was assayed by its ability to immunize mice against SV40-containing ascites tumor cells. When T-antigen- and TSTA-containing preparations were sedimented through sucrose gradients, each antigen had a major peak of activity at 6.7S and minor peaks in other regions. Antiserum against T antigen (from tumor-bearing hamsters) immunoprecipitated TSTA activity. A preparation of T antigen from SV80 cells (an SV40-transformed human fibroblast line), which exhibited only one protein band after sodium dodecyl sulfate-polyacrylamide gel electrophoresis, had TSTA activity when as little as 0.6 µg of protein per mouse was used for immunization. These experiments demonstrate that T antigen, the product of the SV40 early A gene, is capable of inducing specific immunity against transplantation of SV40-transformed tumor cells in mice. (47 refs)

- 79-1008 Fibronectin Expression is Determined by the Genotype of the Transformed Parental Cell in Heterokaryons Between Normal and Transformed Fibroblasts.** (Eng) Laurila, P. (Dept. Pathology, Univ. Helsinki, Helsinki, Finland); Wartiovaara, J.; Stenman, S. *J Cell Biol* 80(1): 118-127; 1979.

The expression of fibronectin (FN), a cell-surface-associated transformation-sensitive glycoprotein, was studied in hetero- and homokaryons of normal and simian virus 40 (SV40)-transformed human fibroblasts (FB). FN was stained with rabbit antiserum against human plasma FN and fluorescein isothiocyanate-conjugated sheep anti-rabbit IgG. Cells were identified under the phase-contrast microscope according to the number of nuclei and degree of cytoplasmic labeling with polystyrene particles. The phenotype of the identified cell was then determined from the distribution and intensity of the FN fluorescence. The fluorescence of surface-associated and intracellular FN was evaluated separately. Normal FB homokaryons had an intense surface-associated and intracellular FN fluorescence similar to that of

unfused cells. Transformed cells and their homokaryons had a minimal surface-associated and a weak intracellular FN fluorescence. In heterokaryons formed between transformed and normal FB, the expression of surface-associated FN fell within 24 hr to the level in transformed cell homokaryons. The change was detectable at 3 hr after fusion and was gene dose-dependent. Intracellular FN expression in the heterokaryons was little affected, compared with that in normal FB homokaryons. The results indicate that the transformed genome determines FN expression in heterokaryons. Whether this is exclusively a result of the dominance of the transformed state or whether it is affected by the state of differentiation of the parental cells is not known. (50 refs)

- 79-1009 Circular, Circular-Linear and Branched Herpes Simplex Virus DNA Molecules from Arginine Deprived Cells.** (Eng) Becker, Y. (Lab. Molecular Virology, Hadassah Medical Sch., Hebrew Univ., Jerusalem, Israel); Asher, Y.; Friedmann, A.; Kessler, E. *J Gen Virol* 41(part 3): 629-633; 1978.

The structure of herpes virus DNA synthesized in arginine-deprived BSC-1 cells infected with the HF strain of herpes simplex virus (HSV) was studied. About 90% of the HSV DNA molecules from arginine-deprived cells had a linear conformation with an av length of 52 µm. The contour lengths of the repeat sequences, long component, and short component were 2.5, 37, and 5.2 µm, respectively. About 1.7% of the linear DNA molecules had the conformation of replicative intermediates of HSV DNA. Two types of circular DNA were noted: one type with a contour length corresponding to a complete genome, and one type with a contour length smaller than genome size. Two new species of HSV DNA were observed: a linear DNA with short and long branches and a contour length of 52 µm; and a circular-linear component of the circular-linear species varied from 4.4 to 32.2 µm, and the circular component ranged from 2.7 to 12.1 µm. In some cases the linear component was 3 to 5 times the contour length of the circular component. (14 refs)

- 79-1010 Isolation of a Nucleocapsid Polypeptide of Herpes Simplex Virus Types 1 and 2 Possessing Immunologically Type-Specific and Cross-Reactive Determinants.** (Eng) Heilman, C. J. (Viral Oncology Program, Frederick Cancer Res. Center, Frederick, MD, 21501); Zweig, M.; Stephenson, J. R.; Hampar, B. *J Virol* 29(1): 34-42; 1979.

The approx 40,000-mol wt polypeptides (p40's) from herpes simplex virus types 1 and 2 (HSV-1 and HSV-2, respectively) were purified by gel filtration and ion exchange chromatography and compared using direct and competition radioimmunoassays. The p40's of HSV-1 and HSV-2 were shown to possess cross-reactive and type-specific determinants. Both determinants apparently resided on the same polypeptide

molecule. Intratypic differences were not detected in the antigenic specificities of the p40's from the different strains of HSV-1 and HSV-2 studied. Antigens produced in pseudorabies virus-infected cells did not exhibit detectable cross-reactivity with the p40's of HSV-1 or HSV-2. The observed cross-reactivity between HSV-1 and HSV-2 p40's and antigens produced in cells productively infected with simian herpesvirus SA8 suggested that SA8 virus and HSV share cross-reactive antigenic determinants. Preliminary studies with human sera indicated that the p40 immunoassay should allow for the accurate determination of antibody levels to HSV-1 and HSV-2 type-specific and cross-reactive antigens in human sera. (16 refs)

79-1011 Enhanced Plating Efficiency of Herpes Virus DNA on Herpes Simplex Virus Type 1 DNA-transformed Cells. (Eng) Colbere-Garapin, F. (Unite de Virologie Medicinale, Institut Pasteur, 75724 Paris Cedex 15, France); Horodniceanu, F. *J Natl Cancer Inst* 62(1): 129-131; 1979.

Hamster cells transformed by sheared herpes simplex virus (HSV) DNA (EH/A44), control cells resulting from the spontaneous transformation of the same primary cell culture (EHT), baby hamster kidney cells transformed by polyoma virus (BHK-21/Py), and hamster cells transformed by human cytomegalovirus (Cx90/3B) were transfected with varying amounts of purified HSV type 1 (HSV-1) DNA, and the efficiency of plating of the HSV-1 DNA was determined. Below 0.0037 μ g of input DNA, the dose-response curves were linear, and the plating efficiency in EH/A44 cells was > 15 times that in EHT and BHK-21/Py cells and 100 times that in Cx90 cells. When the infectivity of HSV-1, HSV-2, and *Herpes eidolon* DNA's tested by transfection in various normal and spontaneously transformed, HSV-transformed, and other virus-transformed cell lines, these DNA's generally plated more efficiently on HSV-transformed cells than did intact virus. Furthermore, HSV-1 and HSV-2 DNA plated more efficiently on HSV-1 DNA-transformed (EH/A44) cells than on control cell types, in contrast to *H. eidolon* DNA. Therefore, it appears that the partial resistance of EH/A44 cells to superinfection by intact HSV can be overcome by transfection with viral DNA's. The high competence of EH/A44 cells for transfection with HSV DNA supports the concept that early events (ie, adsorption, penetration, and uncoating) are involved in the reduced plating efficiency of whole virus on HSV-transformed cells. (11 refs)

79-1012 Reversible Inhibition of the Induction of DNA Polymerase of Herpes Simplex Virus Type 2 in HeLa Cells. (Eng) Nishigori, H. (Dept. Molecular Medicine, Mayo Clinic, Rochester, MN, 55901); Sato, M.; Nishimura, C. *Arch Virol* 58(4): 335-340; 1978.

The effects of 2-mercapto-1-(β -4-pyridylethyl)benzimidazole (MPB) on the induction of herpes simplex virus type 2

(HSV-2)-specific DNA polymerase were studied in HeLa cells. The cells were infected with HSV-2 in the presence of different concentrations of MPB (0, 50, or 75 μ g/ml) for 24 hr, and the DNA polymerase activities were determined. The activity in infected cell lysates was almost completely absent in cells treated with MPB, which indicates that enzyme induction was inhibited, since MPB does not directly inhibit viral DNA polymerase. The MPB must be added within 3 hr after infection to block enzyme induction completely. In HeLa cells infected with HSV-2 in the presence of MPB for 9 hr, washed with medium, and refed with fresh medium, viral DNA polymerase began to appear after 6 hr in new medium. This recovery was prevented by the addition of cycloheximide (100 μ g/ml) or of a low concentration of actinomycin D (0.05 μ g/ml). These results suggest that the appearance of DNA polymerase activity after removal of MPB requires the de novo synthesis of protein and the participation of nucleoli. Although the mechanism of action of MPB remains unknown, it may block the induction of HSV-2 DNA polymerase through its effect on nucleolar function. (16 refs)

79-1013 Persistence of Herpes Simplex Virus Type 1 in Rat Neurotumor Cells. (Eng) Doller, E. (Roche Inst. Molecular Biology, Nutley, NJ, 07110); Aucker, J.; Weissbach, A. *J Virol* 29(1): 43-50; 1979.

A chemically induced rat CNS glioma cell line (C143) was infected with herpes simplex virus type 1 (HSV-1), and the preparation and properties of three lines derived from these cells are described. HSV-1 infection line C143 led to almost complete destruction of the cells. Cells that survived the infection were isolated and shown to produce infectious HSV particles for variable lengths of time in culture ranging from 20 to 57 passages. Even though infectious virus production eventually ceased, the cell lines continued to produce herpes-specified proteins, as measured by immunological techniques. These cells also showed herpesviruslike structures in the electron microscope. The persistently infected cells that produced HSV antigens and bore HSV sequences were resistant to superinfection by HSV-1. The resistance was not due to failure of adsorption of the virus or to the production of interferon by the cells. The nature of the block in HSV replication in these neurotumor cells, which contain and partially express the HSV genome, is unknown, but it may offer an interesting parallel to the known latency of HSV in neural tissues. (22 refs)

79-1014 Relationship of Herpes Simplex Virus Type-2 Antibodies and Squamous Dysplasia to Cervical Carcinoma In Situ. (Eng) Thomas, D. B. (Program Epidemiology and Biostatistics, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104); Rawls, W. E. *Cancer* 42(6): 2716-2725; 1978.

This study was made to investigate further whether herpes simplex virus type 2 (HSV-2) plays a role in the etiology of

cervical neoplasia and to provide additional information regarding the possible etiologic relationship between carcinoma in situ (CIS) and dysplasia. Serum specimens from 75 women with cervical CIS, 84 with squamous dysplasia, and 132 controls who had been interviewed previously and tested for complement-fixing antibodies against a number of organisms were analyzed for HSV-2 antibodies. CIS and severe dysplasia were associated with HSV-2 antibodies. Mild dysplasia was related to evidence of prior infection by *Trichomonas vaginalis*, adenoviruses, and *Mycoplasma pneumoniae*, plus a history of vaginal discharge. Severe dysplasia was less strongly related to these variables. The relative risk of dysplasia increased with the number of different pathogens by which a woman had been infected. It is concluded that HSV-2 may be a cause of CIS, that much dysplasia is a nonspecific reaction of the cervical epithelium to chronic inflammation, and that dysplastic lesions that are caused by HSV-2 and, hence, may be precursors to CIS tend to be distinguished by their severity. The six related case-control studies in the literature have shown a positive association between the presence of HSV-2 antibodies and CIS. In these studies, the strength of the association increased with the severity of the lesion, additional evidence that only some of what is called dysplasia is caused by HSV-2. (30 refs)

- 79-1015 Characterization of an Epstein-Barr Virus-induced DNA Polymerase.** (Eng) Ooka, T. (Departement de Biologie Generale et Appliquee, Universite Claude Bernard-Lyon I, 69621 Villeurbanne, France); Lenoir, G.; Daillie, J. *J Virol* 29(1): 1-10; 1979.

The DNA polymerase induced after iododeoxyuridine (IUdR) treatment of Epstein-Barr virus (EBV) producer (P3HR-I) cells was partially purified, its biological properties were compared with those of cellular DNA polymerases, and its relationship to early antigen (EA) was examined. The addition of IUdR to P3HR-I cell cultures led to a large increase in both EBV-induced DNA polymerase activity and EA-positive cells. This EBV-induced DNA polymerase was separated from cellular α - and β -polymerases by sequential column chromatography on Sepharose 6B, diethylaminoethyl-cellulose, and phosphocellulose, resulting in about 320-fold partial purification. The partially purified enzyme could be distinguished from the cellular DNA polymerases by its activation with salts, its catalytic properties, and its sensitivity of N-ethylmaleimide, phosphonoacetic acid, 9- β -D-arabinofuranosyl-ATP (araATP), and 1- β -D-arabinofuranosylcytosine 5'-triphosphate (araCTP). The viral polymerase showed properties similar to those reported for other herpesvirus DNA polymerases. It exhibited optimal activity for copying activated calf DNA in the presence of 50 mM $(\text{NH}_4)_2\text{SO}_4$ and was resistant to 150 mM $(\text{NH}_4)_2\text{SO}_4$. It utilized with high efficiency template-primer poly(dC)-oligo(dG)₁₂₋₁₈ or poly(dA)-oligo(dT)₁₂₋₁₈, but it failed to copy poly(rA)-oligo(dT)₁₀ and oligo(dT)₁₀, indicating that this enzyme has properties distinct from those of DNA polymerase γ , reverse transcriptase, and terminal deoxynu-

cleotidyl transferase. Phosphonoacetic acid inhibited not only EBV DNA polymerase, but also, to a lesser degree, cellular DNA polymerase α . AraATP did not markedly inhibit viral enzyme activity, but polymerase α was inhibited completely. Both EBV polymerase and polymerase α were inhibited to a similar degree by araCTP. (31 refs)

- 79-1016 Cultured "Hairy Cells" Infected with Epstein-Barr Virus: Evidence for B-Lymphocyte Origin.** (Eng) Lemon, S. M. (Univ. North Carolina Sch. Medicine, Chapel Hill, NC); Pagano, J. S.; Utsinger, P. D.; Sinkovics, J. G. *Ann Intern Med* 90(1): 54-55; 1979.

The origin of a "hairy cell" line (line 4972) established from the spleen of a 30-yr-old black man with leukemic reticuloendotheliosis was studied. Eighty-five percent of the cells contained Epstein-Barr virus (EBV) nuclear antigen and 11% were positive for EBV capsid antigen. The presence of EBV DNA in the cells was confirmed by RNA-DNA hybridization and DNA-DNA renaturation kinetics. The latter technique also demonstrated a 95% homology between the EBV DNA extracted from the hairy cell line and the EBV DNA derived from the P3HR-I African Burkitt's lymphoma cell line. Although evidence suggests a causative role for EBV in African Burkitt's lymphoma, etiologic significance cannot be assigned to the virus found in the hairy cell. No EBV DNA could be detected in three leukemic reticuloendotheliosis tumor specimens, including the spleen from which line 4972 was established. Virus capable of transforming human umbilical cord lymphocytes could not be recovered from the hairy cells. Infection with EBV is a characteristic that hairy cells may share with normal B lymphocytes and is indicative that these cells may be, at least in some situations, of B-lymphocyte origin. (5 refs)

- 79-1017 Epstein-Barr Virus Antibodies in Sudanese Patients with Nasopharyngeal Carcinoma: A Preliminary Report.** (Eng) Malik, M. O. (Pathology Dept., Faculty Medicine, Riyadh Univ., P.O. Box 2925, Riyadh, Saudi Arabia); Banatvala, J.; Hutt, M. S.; Abu-Sin, A. Y.; Hidaytallah, A.; El-Hadi, A. E. *J Natl Cancer Inst* 62(2): 221-224; 1979.

Epstein-Barr viral capsid antigen antibody titers were determined in the sera of 208 Sudanese cancer patients and 18 normal controls by an indirect immunofluorescence technique. Of the patients, 41 had anaplastic nasopharyngeal carcinoma (NPC), 77 had other cancers of the head and neck, 21 had leukemia or malignant lymphoma, 6 had specific granulomas, and 63 had cancers at all other sites. All NPC patients had anti-Epstein-Barr virus (EBV) titers >40 ; 87.9% had titers ≥ 320 and 43.9% had titers $\geq 2,560$. The geometric mean titer (GMT) level of these patients was 1,855. These high titers were independent of age, sex, locality, or tribe. All leukemia and lymphoma patients also had titers $>$

40, although only 33.3% were ≥ 320 and 4.8% $\geq 2,560$. All the remaining groups had significantly more subjects with titers < 40 , fewer with titers ≥ 320 , and very few with titers of $\geq 2,560$. Their GMT was 4-16 times lower than that of NPC patients. These findings lend further support to the hypothesis that NPC and EBV are associated. (23 refs)

79-1018 Cell-Density-Dependence for Growth in Agarose of Two Human Lymphoma Lines and its Decrease after Epstein-Barr Virus Conversion. (Eng) Montagnier, L. (Unite d'Oncologie Virale, Departement de Virologie, Institut Pasteur, Paris, France); Gruest, J. *Int J Cancer* 23(1): 71-75; 1979.

Two Epstein-Barr virus (EBV)-negative Burkitt's lymphoma lines (BJAB and Ramos) and their EBV-converted derivatives were compared with respect to growth in agarose medium. BJAB cells at low concentrations did not grow in agarose, but an abrupt rise in cloning efficiency was observed with concentrations of 3 to 6 $\times 10^5$. BJAB cells converted by the B95/8 or P3HR1 strain of EBV could form colonies at concentrations as low as 5 $\times 10^4$. The max cloning efficiency was higher with the EBV-converted lines. In liquid medium, BJAB cells grew only slightly more slowly than their converted derivatives. The cloning efficiency of both cell types was greatest when pyrolyzed water was used in the agarose, when the agarose concentration was 0.4% in the underlayer and 0.285% in the overlayer, in the presence of 10% fetal calf serum, and in the presence of feeder MRC5 conditioning cells. Similar but even more striking results were obtained when the Ramos line was compared with its EBV-converted derivatives. The difference may be related to a super-transformation state induced by EBV in the converted derivatives. (16 refs)

79-1019 Gibbon Ape Leukemia Virus-Hall's Island: New Strain of Gibbon Ape Leukemia Virus. (Eng) Reitz, M. S. (Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20014); Wong-Staal, F.; Haseltine, W. A.; Kleid, D. G.; Trainor, C. D.; Gallagher, R. E.; Gallo, R. C. *J Virol* 29(1): 395-400; 1979.

A C-type virus, gibbon ape leukemia virus-Hall's Island (GaLV-H), was isolated from a gibbon ape with acute lymphocytic leukemia from a small colony on Hall's Island near Bermuda. It was compared with simian sarcoma virus (SiSV) and other GaLV isolates (GaLV-SF, GaLV-SEATO, and GaLV-Br) by p30 and reverse transcriptase serology and analyses of nucleic acid sequences. Nucleic acid hybridization experiments indicated that GaLV-H was about 60% related to the other GaLV isolates, but only about 20% related to SiSV. RNase T1 oligonucleotide fingerprint analysis suggested that, of the previously described infectious C-type viruses of primates, GaLV-H is most closely related to GaLV-Br. Thus, GaLV-H represents a fifth distinct strain of the infec-

tious primate C-type viruses. It is possible that a substantial portion of the observed difference in hybridization between the RNA of GaLV-H and those of the other isolates was due to differences in RNA sequences coding for the envelope protein (gp70). (26 refs)

79-1020 Hepatitis B Virus Infection and Chronic Liver Disease in Taiwan. (Eng) Chen, D. S. (Dept. Internal Medicine, Natl. Taiwan Univ. Hosp., Taipei, Taiwan 100); Sung, J. L. *Acta Hepatogastroenterol (Stuttg)* 25(6): 423-430; 1978.

The presence of hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs) in 385 patients, most of whom had chronic liver diseases (127 with hepatomas), and 729 healthy adults was determined by reversed passive hemagglutination and passive hemagglutination, respectively. Approx 15% of the healthy adults were HBsAg-positive and 45% were anti-HBs positive, indicating that hepatitis B virus (HBV) infection had occurred in almost two-thirds of the healthy population before adulthood. The prevalences of HBsAg were $> 80\%$ in chronic hepatitis, cirrhosis, and hepatoma, indicating an intimate relationship of these diseases to HBV. On the other hand, the positive rates of anti-HBs in these diseases were far lower than those in healthy people and in patients with other diseases, a situation similar to that in chronic HBsAg carriers. The prevalence of HBsAg in the hepatoma patients was unusually high (82.7%), in contrast to that in patients with other malignancies (11.9%). Hepatoma patients both with and without cirrhosis were found to have a high prevalence of HBsAg, indicating that there is an even more intimate relationship between hepatoma and HBV. (58 refs)

79-1021 Adenovirus Infection and Cytopathic Alterations of Human Cervical Epithelial Cells In Vitro. (Eng) Vesterinen, E. (Cancer Res. Center, Univ. North Carolina, Chapel Hill, NC, 27517); Vaheri, A.; Paavonen, J.; Saksela, E. *Acta Cytol (Baltimore)* 22(6): 566-569; 1978.

To analyze the adenovirus-induced cervical infection in detail, monolayer cultures of human ecto- and endocervical epithelial cells were used as targets for adenovirus infection in vitro. In both types of cultures, adenovirus type 1 resulted in a slowly progressing lytic infection with persistent production of infectious virus, viral antigens, and cytopathic alterations in a fraction of cells. In both cell types, the first morphological alterations were observed 48 hr after inoculation of the cultures with about 1 plaque-forming U/cell. The changes were similar in both cell types. Although many alterations may represent unspecific lesions, nuclear changes consisting of lobulated inclusion bodies seemed to be characteristic. The inclusions were mainly irregular and somewhat diffuse, but as the destruction of the explant colonies spread, more regular large inclusions were seen. The cytoplasm of

adenovirus-altered cells was morphologically normal, but vacuolization could sometimes be seen during the latest phases of the infective cycle. In cultures of ectocervical cells studied during the second week after infection, 5%-10% of the cells were positive in immunofluorescence. In endocervical cultures, a somewhat weaker adenovirus-specific immunofluorescence was seen in about 1% of cells. The alterations produced by adenovirus infection differ from those observed during herpes virus infections, and they may serve as indicators of cervical adenovirus infection in cytologic screening. (16 refs)

- 79-1022 Coincidence of the Promoter and Capped 5' Terminus of RNA from the Adenovirus 2 Major Late Transcription Unit.** (Eng) Ziff, E. B. (Rockefeller Univ., New York, NY, 10021); Evans, R. M. *Cell* 15(4): 1463-1475; 1978.

The map positions and structures of the late promoter and capped 5' terminus of late nuclear and cytoplasmic RNA from the major late transcription unit of adenovirus 2 (Ad2) were analyzed. The data showed that the Ad2 major late promoter and the template for the 5' terminus of capped late transcripts map at the same coordinate within Ad2 DNA. The late promoter was mapped at coordinate 16.5 ± 0.5 by applying the method of nascent chain analysis to short in vivo pulse-labeled nuclear RNA. Polyadenylation and cap formation, two events in messenger RNA (mRNA) synthesis, occurred on unspliced molecules. A nine residue complementarity was shown between the first leader segment and the 3' terminus of 18S rRNA, suggesting that the first leader functions in ribosome binding. Nucleotide sequences from the promoter region were compared with cellular counterparts. Strong homologies at cap sites and splice points suggested that the virus and cell shared closely related mechanisms for mRNA 5' end synthesis and splicing. (31 refs)

- 79-1023 Steps in the Processing of Ad2 mRNA: Poly(A)+ Nuclear Sequences are Conserved and Poly(A) Addition Precedes Splicing.** (Eng) Nevins, J. R. (Rockefeller Univ., New York, NY, 10021); Darnell, J. E. *Cell* 15(4): 1477-1493; 1978.

The order of the steps in the formation of late adenovirus 2 (Ad2) messenger RNA's (mRNA's) was studied. The data indicate that late in Ad2 infection, a series of at least 13 mRNA's arranged in five 3' coterminal groups is derived from the 16-99 transcriptional unit. The posttranscriptional processing involves addition of cap, endonucleolytic cleavage, poly(A) addition, and RNA:RNA splicing. About 20% of the RNA transcribed from each of the five regions containing the 3' mRNA termini is conserved, and all, or most, of the poly(A)-terminated nuclear RNA is conserved. Thus, only one mRNA is made from each transcriptional event in the 16-99 region. Two tentative rules of transcriptional unit de-

sign and mRNA processing were postulated: the RNA polymerase continues past all poly(A) sites in a transcription event; and the first step in processing a primary transcript is cleavage and poly(A) addition. For those transcriptional units containing more than one poly(A) site, the choice of poly(A) would determine the group of mRNA's within which the final choice of mRNA is made. For those transcriptional units containing only one poly(A) site, the addition of poly(A) may be a necessary first step in processing, but the choice of mRNA is made at the splicing step. (64 refs)

- 79-1024 Nucleotide Sequence at the Junction Between the Coding Region of the Adenovirus 2 Hexon Messenger RNA and Its Leader Sequence.** (Eng) Akusjarvi, G. (Inst. Microbiology, Biomedical Center, Box 581, S-751 23 Uppsala, Sweden); Pettersson, U. *Proc Natl Acad Sci USA* 75(12): 5822-5826; 1978.

The nucleotide sequence at the amino terminal end of the gene for the adenovirus type 2 (Ad2) hexon is described, along with its relation to the leader sequence of the hexon messenger RNA (mRNA). For most experiments, an approx 600-nucleotide fragment located between map positions 50.1 and 51.1 was isolated and further cleaved with endonucleases before being end-labeled with polynucleotide kinase. In each case, the labeled fragments were recleaved with *Hae* III to generate fragments labeled at only one end. To determine the sequence immediately leftward of the cleavage site for *Sma* I at position 51.1, end-labeled fragment *Sma* I-D was recleaved with *Bgl* II. The established 139-base pair DNA sequence included an AUG initiator codon located 75-77 nucleotides to the left of the *Sma* I cleavage site and codons for the first 26 amino acids of the hexon polypeptide. Using the purified hexon mRNA as template and separated strands of small restriction enzyme fragments as specific primers, it was possible to copy the complete 5' noncoding region of the hexon mRNA with reverse transcriptase and determine part of its sequence. The region was estimated to be 235 nucleotides long by gel electrophoresis, with the tripartite leader sequence beginning 39 nucleotides to the left of the initiator codon. The DNA sequence at the junction of the leader sequence permitted the formation of secondary structures that may be important for splicing reactions, serving as recognition signals for splicing enzymes. (24 refs)

- 79-1025 Analysis of Human Cancer DNA for DNA Sequences of Human Adenovirus Type 4.** (Eng) Mackey, J. K. (Inst. Molecular Virology, St. Louis Univ. Sch. Medicine, 3681 Park Ave., St. Louis, MO, 63110); Green, M.; Wold, W. S.; Rigden, P. *J Natl Cancer Inst* 62(1): 23-26; 1979.

Samples of human tumor DNA were assayed for adenovirus type 4 (Ad4) DNA sequences by molecular hybridization with in vitro-labeled Ad4 DNA (specific activity = approx

10^7 ^3H cpm/ μg). Hybridizations of 500 cpm Ad4 DNA (0.05 nanograms) and 6 mg tumor DNA/ml (0.3 mg) were carried out in liquid phase. No viral DNA sequences were detected in 31 squamous cell carcinomas of the lung, 5 adenocarcinomas of the lung, 4 oat cell carcinomas of the lung, 4 carcinomas of the stomach, 10 carcinomas of the colon, 3 carcinomas of the kidney, 3 carcinomas of the breast, 2 carcinomas of the ovary, and 6 Hodgkin's lymphomas. Reconstruction experiments (using unlabeled Ad4 DNA added to 6 mg calf thymus DNA/ml) performed under the same conditions as the tumor analyses indicated that the probe detected Ad4 sequences ranging from one copy of approx 5% of the Ad4 genome per cell to one copy of the entire Ad4 genome per every 10th or 20th cell. These results suggest (but do not prove) that none of these tumors were induced by Ad4 and, consequently, that Ad4 presents no carcinogenic risk in human cancers. (30 refs)

79-1026 Adenovirus Type 12 Gene 401 Function and Maintenance of Transformation. (Eng) Ledin-ko, N. (Dept. Biology, Univ. Akron, Akron, OH, 44325); Schaeufele, J.; Soorma, O. *J Virol* 29(1): 250-260; 1979.

Rat (3Y1) and hamster embryo brain cells transformed by wild-type adenovirus type 12 or the DNA-minus temperature-sensitive mutant $\Delta 401$ were characterized at the permissive and nonpermissive temperatures with respect to expression of parameters of the transformed phenotype. The $\Delta 401$ -transformed 3Y1 cells, but not the wild-type transformants, displayed a temperature-sensitive response with respect to morphology, saturation density, growth rate, cloning in soft agar, colony formation on plastic at low cell densities in 1% serum medium, and expression of tumor (T) antigen(s). In temperature shiftdown experiments, the density-dependent inhibition of growth of the $\Delta 401$ -transformed cells was found to be reversible, as was, to some extent, the low efficiency of colony formation at low cell densities in 1% serum. Examination of hamster transformants for their ability to clone in soft agar at permissive and nonpermissive temperatures showed that this property was temperature-dependent, again only in the $\Delta 401$ transformants and not in the wild-type transformants. Alteration in uptake of 2-deoxyglucose or in intracellular cyclic AMP content was not a characteristic of the adenovirus-transformed phenotype in the 3Y1 cells. The findings suggest that an active 401 function is required for maintenance of the adenovirus-transformed cell phenotype. (39 refs)

79-1027 Comparative Study by Immunofluorescence of T and P Antigens Induced by Adenovirus Type 12 in Permissive and Nonpermissive Cells. (Eng) Ribeiro, G. (Unit Virology, Biological Res. Center, Gulbenkian Inst. Science, Oeiras, Portugal); Vasconcelos-Costa, J. *Arch Virol* 58(4): 269-276; 1978.

The development of adenovirus type 12 (Ad12) tumor (T) antigen and of the complex of antigenic early proteins designated as P antigen was studied by immunofluorescence in productively infected human KB cells and abortively infected rabbit kidney (RK-13) cells. The cells were infected with Ad12 at a multiplicity of infection of 2×10^{-2} TCID₅₀/cell. T antigen was detected in both cell types as early as 6 hr after infection. In KB cells, it appeared both as small dots and as short, very thin nuclear flecks and reached a max (>90% of cells being positive) at 18 hr after infection. At the time of max abundance in RK-13 cells, also 18 hr after infection, T antigen formed a net of long, intertwined filaments that completely filled the nuclei. By 24 hr after infection, part of the filaments condensed into a large aggregate that finally was apparently degraded at about 72 hr. T antigen was never observed in the cytoplasm. P antigen was first detected in KB cells 9 hr after infection; up to 18 hr after infection, it was very similar in form to T antigen. By 24 hr after infection, when almost every cell was positive, the nuclei showed one or two large fluorescent bodies comprised of rings or clusters of large balls. P antigen was first detected in RK-13 cells 12 hr after infection and resembled T antigen in KB cells. The later component of P antigen in KB cells is probably a DNA-DNA-binding protein replication complex that is dependent on newly synthesized viral DNA. (23 refs)

79-1028 Identification of Murine Endogenous Xenotropic Retrovirus in Cultured Multicellular Tumour Spheroids from Nude-Mouse-Passaged Nasopharyngeal Carcinoma. (Eng) Crawford, D. H. (Dept. Pathology, Medical Sch., Univ. Bristol, Univ. Walk, Bristol BS8 1TD, England); Achong, B. G.; Teich, N. M.; Finerty, S.; Thompson, J. L.; Epstein, M. A.; Giovanella, B. C. *Int J Cancer* 23(1): 1-7; 1979.

Culturing nude mouse-passaged nasopharyngeal carcinoma (NPC) epithelial cells as multicellular spheroids allowed the definitive identification of endogenous xenotropic retrovirus. Cultured tumor fragments and free cells grown in agar plates formed multicellular tumor spheroids, 40-500 μm in diameter, after 10-14 days. The spheroids continued to grow in size, increased in number by budding, and could be subcultured for up to 6 mo. Histological examination of the spheroids demonstrated a compact outer shell of actively growing epithelial cells surrounding an inner core of loosely packed cells, some of which were degenerating and had pyknotic nuclei. Ultrastructural examination showed large numbers of typical immature C-type virus particles in cytoplasmic spaces and between the cells within the spheroids. After bromodeoxyuridine treatment, the spheroids generally contained even more numerous C-type particles. Experiments in which tumor spheroids were cocultivated with monolayer cell lines suggested that the virus produced by the cells in the NPC spheroids infected the monolayer cells, and thus had properties in common with xenotropic murine type-C virus. Further experiments suggested that the origin of the type-C virus was

the nude mouse host through which the NPC tumor cells had passed. (21 refs)

- 79-1029 Antigen Associated with Oncornavirus D in Continuous Cultures of Human and Animal Cells.** (Rus) Posevaia, T. A. (D. I. Ivanovskii Inst. Virology, Moscow, USSR); Kosiakova, N. P.; Tsareva, A. A.; Novokhatskii, A. S. *Vopr Virusol* (6): 714-717; 1978.

A series of continuous and primary trypsinized cultures of human and animal cells were analyzed for the presence of a new antigen associated with oncornavirus D. Specific sera against new antigen reacted with antigens isolated from HeLa, V, KB, VERO, and CV-1 cells, but showed no reaction with FS-4, L-929 and SIRC cells. Antigen was also present in HEPv-2 and J-96 cells. The new antigen could not be detected in cultures infected with oncogenic viruses other than oncornavirus D. (16 refs)

- 79-1030 Comparative Study of Proteins of Oncornaviruses A and D in Continuous Culture of Human Cells J-96 by Isoelectric Focusing and Electrophoresis in Polyacrylamide Gel.** (Rus) Kitsak, V. Ia. (Central Inst. Advanced Training Physicians, Moscow, USSR); Moisiadi, S. A.; Delimbetova, G. A.; Dotsenko, V. L.; Krispin, T. I. *Vopr Virusol* (6): 718-722; 1978.

Isoelectrofocusing and polyacrylamide gel electrophoresis were employed for analysis of the proteins from intracellular

virion type A and extracellular virion type D produced by human lymphoblastoid J-96 cells. It was found that the proteins of virion type D were localized in zones with pH of 3.7, 4.0, 4.4, 4.7, 5.6, 6.5, 8.1, 9.45 and 10.0, compared with 4.0, 4.9, 6.7, 7.3, 9.0, 9.45 and 10.0 for protein from virion type A. Type A virions did not contain proteins with mol wt of 10,000, 12,000, 15,000 or 27,000 daltons. These findings, which confirm previously reported data on the differences between A and D virions from HEP-2 cells, indicate that type A virions are not the precursors of type D virions. (9 refs)

See also:

- *(Rev.): 79-0621, 79-0622, 79-0623, 79-0624, 79-0625.
- *(Chem.): 79-0806, 79-0856, 79-0863, 79-0871, 79-0885.
- *(Phys.): 79-0939.
- *(Immun.): 79-1031, 79-1044, 79-1049.
- *(Path.): 79-1067, 79-1074.
- *(Epid.-Biom.): 79-1134.

- 79-1031** Correlated Expression of a B-Lymphocyte-specific Glycoprotein (gp27/35) and the EBV Receptor/C3 Receptor Complex in Sublines from the Same Burkitt Lymphoma. (Eng) Klein, G. (Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden); Hyman, R.; Trowbridge, I. *Int J Cancer* 23(1): 37-41; 1979.

The relationship between a B-lymphocyte-specific glycoprotein (gp27/35) and the Epstein-Barr virus (EBV) receptor/complement (C3) receptor complex was reexamined in virus-producer and nonproducer sublines derived from the Burkitt's lymphoma line Jijoye and its P3HR-1 clone. These sublines were previously found to differ in the expression of EBV receptors and, in parallel, C3 receptors. Quantitative absorption studies demonstrated a close parallelism between the expression of the EBV receptor-complement receptor complex and the glycoprotein. Both were expressed on the cell line from which the cytopathic-virus-producing P3H3 line is derived. However, both were greatly reduced in the P3H3 line itself and in several other sublines derived from P3H3 cells. Both gp27/35 and EBV-complement receptors reappeared in parallel in the "revertant" P3HR-1 NP line and, more strongly, in line BU-P3HR-1. The results favor a relationship between gp27/35 and EBV/C3 receptor expression. (15 refs)

- 79-1032** *Helix pomatia* A Hemagglutinin: Selectivity of Binding to Lymphocyte Surface Glycoproteins on T Cells and Certain B Cells. (Eng) Axelsson, B. (Dept. Immunology, Univ. Stockholm, S-10691 Stockholm, Sweden); Kimura, A.; Hammarstrom, S.; Wigzell, H.; Nilsson, K.; Mellstedt, H. *Eur J Immunol* 8(11): 757-764; 1978.

The surface structures of human and mouse lymphocytes responsible for binding to *Helix pomatia* A hemagglutinin (HP) were studied. Lymphocytes were surface-labeled by lactoperoxidase-catalyzed iodination, or by galactose oxidase oxidation followed by reduction with tritiated sodium borohydride. The labeled cells were then lysed with detergent. Proteins binding to HP were isolated by affinity chromatography on HP-Sepharose and analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and autoradiography. A major cell-surface glycoprotein [gp: mol wt 150,000 (150K)] using reducing conditions on human lymphocytes was responsible for >90% of all HP binding. It was present on normal and malignant thymus-derived lymphocytes, on chronic lymphocytic leukemia cells, and on cells of a null cell leukemia line, an unidentified leukemia line, a lymphoblastoid cell line of B origin, and a stem cell lymphoma line. It was absent from lines of more differentiated

B cells (4 Burkitt's and non-Burkitt's lymphoma lines, 1 myeloma line) and from a histiocytic leukemia line. However, two of the four B lymphoma lines and the myeloma line displayed a 200K HP-binding surface gp. Biosynthetic labeling indicated that the 150K gp was synthesized by the lymphocytes. The results from surface- and biosynthetic-labeling established that the 150K protein is a sialylated gp. Mouse T cells (normal and malignant) but not normal adult B cells expressed a 130K HP-binding surface gp. The 150K HP-binding surface gp on the human cells may be considered a differentiation marker. (55 refs)

- 79-1033** Recovery from Postoperative Immunosuppression: Efficacy of an Immunorestorative Drug. (Eng) Lundy, J. (Dept. Surgery, Univ. Connecticut Health Center, Farmington, CT); Lovett, E. J.; Conran, P. B. *Surg Forum* 29: 3-5; 1978.

Thiabendazole restored and impaired cell-mediated immunity of thiopental-, thiopental-halothane-, and thiopental-halothane- + surgically treated (hind limb amputation) C57BL/6 female mice; ie, it resulted in the recovery of normal mixed lymphocyte culture kinetics. (2 refs)

- 79-1034** Humoral and Cell-mediated Immune Competence of High-Cancer-Risk Canine Breeds. (Eng) Dorn, C. R. (Dept. Veterinary Preventive Medicine, Coll. Veterinary Medicine, Ohio State Univ., Columbus, OH, 43210); Heuschele, W. P. *Am J Vet Res* 39(12): 1932-1935; 1978.

The possibility that dogs with a high cancer risk (ie, boxers and terriers) might have breed-associated immune response anomalies was examined. Immune competence of four boxers and four terriers was compared with that of four beagles, which do not have a high cancer risk. There was no difference between the breeds in their humoral immune competence, as measured by hemagglutinating antibody response to sheep RBC, lymphocytotoxic antibody response following allogeneic skin grafting, and antibody activity following the injection of bacteriophage ϕ X-174. All dogs developed a hemagglutinin titer of 1:128 or greater by day 14, except for one boxer dog. The phage was cleared from the peripheral blood by the fourth day in all beagles, all terriers, and three boxers. In one boxer, the phage had cleared by the seventh day. Cytotoxic antibody against donor lymphocytes was detected in three beagles, three boxers, and four terriers. Following challenge exposure with purified protein derivative, all BCG-sensitized dogs developed a positive reaction of 10 mm or greater, the

reactions being as high as 16 mm. There was no consistent breed difference. Tritiated thymidine incorporation by phytohemagglutinin-purified-stimulated lymphocytes varied as greatly among dogs of one breed as it did between breeds. The mean stimulation indices for the three breeds were not significantly different. These indirect measurements of immune competence that may affect the development of neoplasms do not support either the hypothesis of immune surveillance or of immune enhancement. Temporal and other factors may have prevented the detection of an association between high-cancer-risk breeds and aberrant immune responses. (42 refs)

- 79-1035 Hybridization of T Lymphocytes: Characterization of a Suppressor Factor Produced by a Hybrid T Cell Line in Mice.** (Eng) Holliman, A. (Inst. Animal Physiology, Babraham, Cambridge CB2 4AT, England); Taussig, M. J. *J Physiol (Lond)* 284: 5P-6P; 1978.

The supernatant of a hybrid T-cell line produced by fusion of azaguanine-resistant thymoma BW5147 cells to spleen cells of mice immunized with sheep RBC (SRBC) suppressed the antibody response to SRBC in culture 80%-90%. The suppressive factor suppressed the response to SRBC more actively than that to other antigens and it could be absorbed specifically by SRBC. It is not an immunoglobulin, it carries determinants of the murine major histocompatibility gene complex, and it has two chains of mol wts 80,000 (80K)-90K and 20K-25K. (6 refs)

- 79-1036 Correlation Between Natural and Antibody-dependent Cell-mediated Cytotoxicity Against Tumor Targets in the Mouse. I. Distribution of the Reactivity.** (Eng) Santoni, A. (Istituto di Farmacologia, Università degli Studi di Perugia, 06100, Perugia, Italy); Herberman, R. B.; Holden, H. T. *J Natl Cancer Inst* 62(1): 109-116; 1979.

The expression of natural killer (NK) activity and levels of antibody-dependent cell-mediated cytotoxicity (ADCC) against RBL-5 TC mouse tumor cells (Rauscher murine leukemia virus-induced ascites cell line of C57BL/6 origin) coated with an alloantiserum were compared. NK activity and ADCC were tested simultaneously in an 18-hr ⁵¹Cr-release cytotoxicity assay (CRA), but characteristics of NK activity were the same when the CRA was performed for 4 hr. In normal spleens of individual mice, NK activity and ADCC levels fluctuated in a parallel manner. Activities were high in C3Hf, CBA, and several strains of nude mice, intermediate in BALB/c and C57BL/6 mice, and low in SJL mice. Peak activities for both functions occurred in 4- to 9-wk-old mice. Activity was highest in cells of the spleen and peritoneal cavity. Intermediate activities were found in lymph node and bone marrow cells, the lowest activities in thymus cells. Ip injection of lymphocytic choriomeningitis virus into several strains of mice caused a marked stimulation of both NK and

ADCC activities, whereas the presence of murine sarcoma virus-induced tumors depressed these activities. Although the two effector functions produced synergistic results against target cells sensitive to NK, cell susceptibility to NK activity was not a prerequisite for susceptibility to ADCC; target cells resistant to NK activity could be lysed when they were coated with alloantibody. The close correlation between NK cell and ADCC activity indicates that natural cell-mediated cytotoxicity is possibly due to the arming of K cells with natural antibodies. (59 refs)

- 79-1037 Monovalent Antibodies Directed to Transformation-sensitive Membrane Components Inhibit the Process of Viral Transformation.** (Eng) Lingwood, C. A. (Hosp. Sick Children, Toronto, ON M5G 1X8 Canada); Ng, A.; Hakomori, S. *Proc Natl Acad Sci USA* 75(12): 6049-6053; 1978.

The inhibition of the expression of the oncogenic phenotype by monovalent antibodies (Fab) directed to the transformation-sensitive cell-surface components galactoprotein a (Gap a) or gangliosides GM₁ or GM₂ is described. Mouse 3T3 cells infected with murine sarcoma virus were not transformed in terms of morphology or sugar uptake when they were cultured in the presence of Fab directed to GM₁ or Gap a. The inhibitory activity of these cell-surface ligands was not related to cell growth inhibition, because the Fab to globoside and divalent concanavalin A were growth inhibitory but not transformation inhibitory. Neither anti-GM₁ nor anti-Gap a Fab inhibited virus production. The inhibitory activity of anti-ganglioside and anti-Gap a Fab was also assessed in a normal rat kidney cell line transformed by a temperature-sensitive mutant of avian sarcoma virus (NRK/LA25). In this cell line, GM₁ (but not GM₂) and Gap a were transformation-sensitive cell-surface components. Expression of the transformed phenotype (changes in morphology, growth in 0.3% agar) at the permissive temperature was inhibited by preincubating the cells with anti-GM₁ or anti-Gap a Fab. GM₁ labeling of NRK/LA25 cells decreased at the permissive temperature, whereas preincubation of the cells with anti-Gap a, which induces inhibition of transformation after a temperature shift, prevented the decrease in GM₁ labeling. The data suggest a possible correlation between GM₁ and Gap a expression. Application of Fab to these transformation-sensitive components may prevent changes of these components on cell surfaces and thus may result in abortion of the phenotypic expression of transformation, even though the transforming gene (*src*) has been activated. These results indicate that pericellular structures influence gene expression. (44 refs)

- 79-1038 Immunopathogenicity and Oncogenicity of Murine Leukaemia Virus. IV. Antinuclear Antibody Response and Tumour Induction in B10.A Recombinant Mice.** (Eng) Croker, B. P. (Dept. Pathology, Box 3712, Duke Univ. Medical Center, Durham, NC, 27710); Bourdon,

M.; McConahey, P. J.; Dixon, F. J. *J Immunogenet* 5(6): 401-409; 1978.

Antinuclear antibody (ANA) production following murine leukemia virus (MuLV)-Scripps infection of B10.A and B10.A recombinant (2R, 3R, 4R, and 5R) mice was studied in an effort to identify the nuclear antigen(s) and the subregion of the *H-2* complex that might be involved in regulation of antibody type and titer. The mice could be divided into high- and low-responder groups. Compared with controls, however, all infected animals had significant increases in ANA titer and incidence. 3R and 5R mice had the highest incidence and titers up to 10 times those of the other groups, with the geometric mean titers of the females being significantly higher than those of the males. Most of the high ANA antibody was attributable to anti-histone antibody. A high response was associated with the H-2b haplotype and recombinant strains that were identical at the *I-A* subregion derived from H-2b parental stock. A low response was associated with the *I-A* subregion derived from the H-2k haplotype. Most infected mice of all groups had significantly elevated serum p30 and gp70 levels when tested by radioimmunoassay, and 72%-80% developed lymphomas. Elevated p30 levels were correlated directly with gp70 levels and inversely with tumor latency. Glomerulonephritis developed in 4%-28% of each infected group. No clear genetic basis could be established for glomerulonephritis incidence, serum p30 or gp70 levels, or latency of lymphoma development. (23 refs)

79-1039 Digestion of the Fifth Component of Complement by Leukocyte Enzymes: Sequential Generation of Chemotactic Activities for Leukocytes and for Tumor Cells. (Eng) Orr, F. W. (Dept. Pathology, Univ. Connecticut Health Center, Farmington, CT, 06032); Varani, J.; Kreutzer, D. L.; Senior, R. M.; Ward, P. A. *Am J Pathol* 94(1): 75-83; 1979.

The generation of chemotactic activity (CTA) for WBC and tumor cells by incubating the fifth component of complement (C5) with WBC enzymes was studied using the Walker carcinosarcoma (maintained as an ascites tumor), neutrophilic WBC from rabbits, and complement from normal human serum. The supernatant fluids from suspensions of human neutrophils that had ingested opsonized zymosan particles generated CTA for WBC and for tumor cells when incubated with C5. The generation of leukotactic activity (LTA) occurred 2-5 min after the onset of incubation. CTA for tumor cells appeared after 60 min, and its appearance was accompanied by a fall in LTA. LTA was also generated from the third component of complement (C3) after 2 min of similar treatment, but generation of CTA for tumor cells was not observed. The results of treating C5 with the purified lysosomal enzymes cathepsin G and elastase as well as with WBC granule extracts were similar. There was an initial generation of LTA that was followed by a decline in this activity and the generation of CTA for tumor cells. The generation of CTA's from C5 was blocked by prior treatment of WBC

preparations with Trasylol, a protease inhibitor. The interaction between C5 and WBC enzymes could occur readily in injured tissues or at sites of inflammatory responses, and it suggests a possible mechanism by which the development of metastatic lesions may be promoted at sites of tissue injury or inflammation. (24 refs)

79-1040 The Genetics of Teratocarcinoma Transplantation: Tumor Formation in Allogeneic Hosts by the Embryonal Carcinoma Cell Lines F9 and PCC3. (Eng) Avner, P. R. (Laboratoire d'Immunologie et Virologie des Tumeurs, Hopital Cochin, U152, Paris 75014, France); Dove, W. F.; Dubois, P.; Gaillard, J. A.; Guenet, J. L.; Jacob, F.; Jakob, H.; Shedlovsky, A. *Immunogenetics* 7(2): 103-115; 1978.

Two cultured lines of murine teratocarcinomas, F9 and PCC3, were grafted to a variety of allogeneic hosts, and the host strains were classified by their resistance or sensitivity to these carcinomas. Strains most sensitive to tumor induction by F9 were A/He, DBA/2, and SJL/J, each of which carries a histocompatibility (*H-2*) haplotype distinct from that of the syngeneic strain, 129. Strong *H-2* differences, therefore, are not sufficient to cause rejection of F9 tumors. Strain DBA/2 was sensitive to tumor production by PCC3, but A/He and SJL/J were completely resistant. The sensitivity of the rejection mechanism to sublethal x-irradiation and the transfer of resistance using lymphoid reconstitution of lethally irradiated animals indicate that the rejection of F9 and PCC3 has an immunological basis. Allograft rejection appears to be determined by a small number of loci. On the basis of F_1 and backcross analysis, resistance of B6 (an F9-resistant allogeneic strain) to F9 seems to be determined by a single recessive factor. B6 resistance to PCC3 seems to be determined by two or three independent loci. A/He resistance to PCC3 appears to be under the control of a single recessive factor linked to *H-2*. The fact that sensitive strains were readily found implies that the allograft rejection loci in mice are not highly polymorphic. Tumor resistance of strains C57BL/6 and AKR appears to result from the interaction of dominant or semidominant factors in the *H-2* region with other recessive elements in the genetic background. (26 refs)

79-1041 Facultative Phagocytosis by Leukemic B-Lymphocytes: Further Proof of the B-Cell Nature of Hairy Cells. (Eng) Catovsky, D. (M.R.C. Leukemia Unit, Royal Postgraduate Medical Sch., Du Cane Road, London W12 0HS, England); Sperandio, P.; O'Brien, M. In: *Recent Results Cancer Res* 64: 208-212; 1978.

In view of the suggestion that hairy cells may correspond to B lymphocytes with phagocytic properties, the phagocytic capacity of lymphocytes from patients with B-lymphoproliferative diseases other than hairy cell leukemia (leukemic reticuloendotheliosis) was studied. When incubated with

fresh human serum and latex particles approx 0.8 μ in diameter, approx 15% of the lymphocytes from three cases of prolymphocytic leukemia and nine cases of chronic lymphocytic leukemia were phagocytic. The phagocytosis was dependent upon the presence of serum. The predominant cell type (> 90%) in these samples was a leukemic lymphocyte with surface immunoglobulin and/or the ability to bind mouse RBC. In most cases, light and electron microscopy usually identified one or two ingested latex particles per cell, but in two cases 17%-30% of the lymphocytes had ingested three or more particles. The degree of phagocytosis correlated significantly with the ability to bind latex particles to the cell surface. This study demonstrates the presence of phagocytic leukemic B lymphocytes in addition to hairy cells, and should strengthen the evidence that hairy cells are lymphocytes in the pathway of B-cell differentiation. (21 refs)

79-1042 Multiple Heavy Chain Isotypes on the Surface of the Cells of Hairy Cell Leukemia. (Eng)

Burns, G. F. (Dept. Haematological Medicine, Univ. Clinical Sch., Hills Rd., Cambridge CB2 2QL, England); Cawley, J. C.; Worman, C. P.; Karpas, A.; Barker, C. R.; Goldstone, A. H.; Hayhoe, F. G. *Blood* 52(6): 1132-1147; 1978.

The mononuclear cells of 15 patients with hairy-cell leukemia were studied for expression of surface membrane immunoglobulin (SIg). SIg of restricted light chain type (10 K:5 λ) was found in all cases. As for heavy chain isotype expression, in seven cases the cells expressed only IgG (6 κ , 1 λ : Type I); seven cases showed three or four isotypes that always included both M and D (3 κ , 4 λ : Type II), and one case showed the combination of M and D alone (κ : Type III). Although wide variations were observed in the percentage of SIg expression and in the relative proportions of the different heavy chain isotypes (Type II) for a single patient at different times, the cells maintained the same isotypes, and the major heavy chain type was consistently expressed on approx the same percentage of cells as bore the exclusive light chain type. SIgD was reexpressed slowly after stripping. The demonstration of cytoplasmic IgG, the presence of IgG in the supernatant of cultured cells, and the observed increase in SIgG rosette formation with time in culture suggested that at least some hairy cells secrete IgG. The presence of multiple heavy chain isotypes on hairy cells seems to place them late in B cell ontogeny. (59 refs)

79-1043 Terminal Deoxynucleotidyl Transferase (TdT), Cytochemistry, and Membrane Receptors in Adult Acute Leukemia. (Eng) Gordon, D. S. (Immunology Div., Bureau Labs., Center Disease Control, 1600 Clifton Road, N. E., Atlanta, GA, 30333); Hutton, J. J.; Smalley, R. V.; Meyer, L. M.; Vogler, W. R. *Blood* 52(6): 1079-1088; 1978.

Terminal deoxynucleotidyl transferase (TDT) activity, immunologic membrane markers, and cytochemical reactivity

were examined in blasts from 80 adults with acute leukemia. TDT was uniformly elevated in all 8 patients with null-cell and T-cell lymphoblastic leukemia, in both patients with null-cell lymphoma, and in 3/27 patients with acute myeloblastic leukemia. TDT activities were low in 24/27 patients with acute myelomonocytic, acute monocytic, and lymphoma leukemia of B- or T-cell type. Blasts from 17 patients did not show distinctive patterns of cytochemical staining; these patients were classified as having acute undifferentiated leukemia. For nine of these patients there was disagreement within a panel of four hematologists as to whether the leukemia should be classified morphologically as lymphoid or nonlymphoid. Especially in such cases, the use of cytochemical techniques, immunologic membrane markers, and TDT determinations offer objective methods for diagnosis of acute leukemia and are likely to be of clinical relevance. (27 refs)

79-1044 Angioimmunoblastic Lymphadenopathy: Evolution to a Burkitt-Like Lymphoma (Meeting Abstract). (Eng) Mazur, E. M. (Dept. Medicine, Yale Univ. Sch. Medicine, New Haven, CT); Lovett, D. H.; Enriquez, R. E.; Papac, R. J. *Clin Res* 26(4): 619A; 1978. (no refs)

79-1045 Physical Association of Histocompatibility Antigens and Tumor-associated Antigens on the Surface of Murine Lymphoma Cells. (Eng) Callahan, G. N. (Dept. Molecular Immunology, Scripps Clinic and Res. Foundation, 10666 N. Torrey Pines Road, La Jolla, CA, 92037); Allison, J. P.; Pellegrino, M. A.; Reisfeld, R. A. *J Immunol* 122(1): 70-74; 1979.

Serologic and immunochemical techniques were used to characterize plasma membrane antigens of the murine estrogen-induced lymphoma 6C3HED. Syngeneic C3H/HeJ anti-6C3HED antisera were prepared and were shown by cytotoxicity, absorption, and immunoprecipitation tests to be specifically reactive with the lymphoma cells. These sera, therefore, appeared to detect a tumor-associated antigen (TAA) of the 6C3HED lymphoma. Alloantisera to H-2.23 antigens were unreactive with intact lymphoma cells by cytotoxicity and absorption assays. However, H-2.23 antigens were detectable in tumor cell lysates by inhibition of cytotoxicity and immunoprecipitation. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) of immunoprecipitates of radiolabeled tumor cell extracts obtained with anti-6C3HED and anti-H-2.23 antisera gave patterns that were essentially identical and had peaks corresponding to proteins with mol wts of 70,000, 45,000, and 12,000. Antigens reactive with both antisera were found to be present on the cell surface. An immunoadsorbent of insolubilized anti-6C3HED removed H-2.23 antigens detectable in lymphoma extracts but had no effect on H-2.23 antigens in normal splenocyte extracts. These data indicate that H-2.23 and TAA are physically associated on 6C3HED cells. This association might be important in the development of

host immunity or in the breakdown of some of the normal cell-cell interactions and control processes that accompany tumorigenesis. (21 refs)

- 79-1046 Hodgkin's Disease. T-Cell Defect in Patients in Complete Remission.** (Fre) Lang, J. M. (Clinique des Maladies du Sang, Centre Hospitalo-Universitaire de Strasbourg, 1, place de l'Hopital, 67005 Strasbourg Cedex, France); Bigel, P.; Oberling, F.; Mayer, S. *Sem Hop Paris* 54(37-40): 1155-1158; 1978.

The T-lymphocyte level was studied in 11 patients (6 men, 5 women) with Hodgkin's disease in complete remission 6-72 mo after the end of 0.5-3 yr of maintenance therapy. Seven patients were initially in Stages III and IV. The peripheral blood lymphocyte count was $< 1,200/\text{mm}^3$ in 5/11 patients. The absolute numbers of erythrocyte (E)-rosette-forming T-lymphocytes were reduced in 8 patients ($248-595/\text{mm}^3$), and the active E-rosette count was reduced in 3/7 patients tested (19%-26%, vs a normal value of 37%). The EAC (erythrocyte antibody complement) rosette count was slightly increased in two patients only (37%, vs a normal value of 24%). In vitro stimulation with a suboptimal dose of phytohemagglutinin was studied in 9 patients and in 19 healthy controls. A statistically significant deficiency of lymphocyte transformation was found that may be due to a membrane change rather than to a true decrease in this reaction. (20 refs)

- 79-1047 Autoimmune Hemolytic Manifestations Associated with Hodgkin's Disease.** (Ita) Boccardi, V. (Istituto di Patologia Medica I, Universita, Rome, Italy); Girelli, G.; Anselmo, A. P.; Mandelli, F. *Recent Prog Med (Roma)* 64(4): 446-454; 1978.

The association of autoimmune hemolytic anemia (AHA) with Hodgkin's disease (HD) was studied in 100 patients with HD. AHA was found in seven cases (4 men and 3 women). Twenty-seven patients were kept under observation because of anemia: AHA was diagnosed in 4 of them. The other 73 patients were subjected to systematic screening for signs of autoimmunization regardless of anemia; AHA was found in 3 of them. Six of the seven patients presented with anemia 2-7 yr after the onset of HD, the seventh patient developed HD 3 yr after the onset of chronic idiopathic anemia. AHA preceding HD can be explained by the immune surveillance theory, according to which the defect responsible for the insurgescence of the neoplasia resides in the inability to terminate the lymphoproliferative process induced by an antigenic stimulation. There is as yet no satisfactory theory to explain AHA associated with HD given the diversity of chronology between the two conditions. (56 refs)

- 79-1048 Hematologic Changes During Spleen Colony Development in Nonirradiated Mice.** (Eng) Tamai, M. (Inst. Cancer Res., Medical Sch., Osaka Univ., Nakanoshima 4-chome, Kita-ku, Osaka 530, Japan); Kitamura, Y. *Blood* 52(6): 1148-1155; 1978.

The mechanism of spleen colony formation in nonirradiated mice was investigated in a time-course study. When the spleen cells of C57BL mice immunized against CBA-T6T6 mice were injected into nonirradiated BT6F₁ (C57BL x CBA-T6T6) hybrid mice, the number of hematopoietic stem cells [colony forming unit-stem cells (CFU-S) of C57BL mouse origin that settled in the spleen of the BT6F₁ mice continued to decrease in the first 9 days and then started to increase, with a doubling time of about 36 hr. Colonies were detected on the surface of the spleen 16-22 days after the cell injection. The slower appearance of spleen colonies in nonirradiated mice (compared with 6-10 days in the irradiated animals) appears to be due to the delayed start of differentiation and to the prolonged doubling time of CFU-S in nonirradiated mice. It is suggested that CFU-S are stimulated into proliferation to repair the decrease of CFU-S caused by immune reactions between host and donor cells, that donor CFU-S replace host CFU-S during the first 9 days after injection of parental spleen cells, and that subsequently, the donor CFU-S can initiate growth like CFU-S injected into lethally irradiated mice. (17 refs)

- 79-1049 Serological Identification of Neoantigens on Mouse Fibroblasts Which Have Undergone "Spontaneous" Malignant Alteration In Vitro.** (Eng) Wil-lumsen, B. M. (Fibiger-Lab., Ndr. Frihavns-gade 70, DK. 2100 Copenhagen 0, Denmark); Ulrich, K.; Kieler, J. *Int J Cancer* 23(2): 209-216; 1979.

Two malignant cell lines result from the spontaneous transformation of ST/a mouse lung fibroblasts in vitro. ST-L1 cells produce tumors only in newborn or immunodepressed syngeneic (SG) mice and ST-L22 cells produce tumors in SG hosts irrespective of age and immunocompetence. Both lines produce nontransforming C-type virus. Neoantigens expressed on ST-L1 cells were analyzed by characterizing the reactivities present in SG anti-ST-L1 antiserum (obtained by hyperimmunizing ST/a mice with an sc injection of ST-L1 cells). Sera from mice that rejected ST-L1 showed reactivity toward the structural murine leukemia virus proteins gp70 and p15(E). Radioimmunoassay showed that ST-L1 and ST-L22 contained the same amount of p30 determinants, but that the latter contained a threefold lower concentration of gp70 determinants. Upon gel electrophoresis, there was a qualitative difference in the mobility of the glycoproteins found in virus particles from both lines. These quantitative and qualitative differences in gp70 expression may account for the different immunogenicity of the cell lines in SG hosts, in which only ST-L1 cells give rise to antibodies toward gp70. However, the complete absorption of anti-ST-L1 reactivity

by large amounts of ST-L22 shows that all antigenic determinants in ST-L1 are present in ST-L22. Either the presentation of the antigens is changed markedly in ST-L1 cells, leading to a disproportionately increased immunogenicity of gp70, or the rate at which gp70 is shed from the cell surface may be higher on ST-L1 cells than on ST-L22 cells. No virus-induced nonviral antigens or serologically detectable, cellularly determined neoantigens were expressed on ST-L1 cells. ST-L1 cells evoke a humoral and a rejection response when injected into SG-mice. It is not known whether identical antigens trigger these responses. (32 refs.)

- 79-1050 Morphology of Lymphoreticular Tissues in Mice with Reticulosarcoma.** (Eng) Pavelic, Z. P. (Dept. Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY, 14263); Boranic, M.; Pavelic, K. *Exp Pathol (Jena)* 15(5): 288-295; 1978.

Transplantation of a syngeneic reticulosarcoma with weak transplantation antigenicity into C57BL mice produced a vigorous histological response in regional lymph nodes and a slight response in nonregional lymph nodes and spleen. Mesenteric lymph nodes and the thymus did not respond. Morphological and gravimetric changes indicated that both regional and nonregional lymph nodes and the spleen take part in the host immune response. (14 refs)

- 79-1051 Evidence for the Expression of Human Tumor-specific Antigens Associated with β_2 -Microglobulin in Human Cancer and in Some Colon Adenomas and Benign Breast Lesions.** (Eng) Thomson, D. M. (Montreal General Hosp. Res. Inst., 1650 Cedar Ave., Montreal, Quebec, Canada H3G 1A4); Tataryn, D. N.; O'Connor, R.; Rauch, J.; Friedlander, P.; Gold, P.; Shuster, J. *Cancer Res* 39(2, part 1): 609-611; 1979.

The blocking tube leukocyte adherence inhibition (LAI) assay was used to monitor the purification of human tumor-specific antigens (TSA's) from colon and breast neoplasms and malignant melanoma. An attempt was made to determine if some benign breast tumors and adenomatous polyps express the same organ type-specific neoantigens as do cancers derived from the same organ. The tumor antigens were specific for the organ from which the cancer arose and the histopathology of the cells of origin. Immunochemical studies revealed that TSA's could be water-solubilized from cancer cell membranes by limited papain digestion; on Sephadex G-150 chromatography, most of the TSA eluted in the mol wt range 70,000-150,000. Affinity chromatography with anti-human β_2 -microglobulin (β_2m) antiserum indicated that the TSA's contain a β_2m subunit. The specificity of binding of the TSA to the anti- β_2m immunoadsorbent affinity column and the immunologically specific abrogation of LAI activity were shown. Some patients with either adenomatous

polyps or benign breast disease showed LAI activity to phosphate-buffered saline extracts of colon and breast cancer, respectively, but did not react to extracts of normal colon mucosa or breast tissue. Moreover, the LAI-reactive WBC were blocked by the papain-soluble TSA's from colon and breast cancer, respectively, purified by anti- β_2m chromatography. These studies suggest that some "benign" lesions express TSA's before the appearance of morphological evidence of cancer. They also indicate that the putative TSA's of cancers of different organs are similar in subunit structure, size, and genetic linkage and have some unexplained relationship to organ definition. (30 refs)

- 79-1052 Suppression of Malignancy in Mouse-Man Hybrid Cells.** (Eng) Louis, C. J. (Dept. Pathology, Univ. Melbourne, Austin Hosp., Heidelberg, Victoria, Australia); Rose, G. B. *Pathology* 10(4): 343-350; 1978.

Somatic cell hybrids were prepared by fusing malignant mouse melanoma cells (PG19) with diploid human lymphocytes and fibroblasts in the presence of inactivated Sendai virus. Clones of hybrid cells differed with respect to their number of chromosomes; in particular, human chromosomes (HuC) were preferentially lost and mouse chromosomes retained. Hybrid clones containing a range of HuC were selected and assayed for tumorigenicity in female nude mice, and the presence or absence of specific HuC was correlated with malignancy. PG19 cells (1×10^5 sc) produced progressive tumors in 5/5 nude mice. Normal human lymphocytes and normal human fibroblasts (both 1×10^6 sc) failed to produce tumors. No hybrids from PG x fibroblast crosses (1×10^6 cells sc) induced tumors in nude mice over a 4-mo period. Only PG19 x lymphocyte hybrids, which contained six or less HuC, produced tumors, the tumor yield being inversely related to the number of HuC present. However, the overall tumorigenicity was considerably reduced from that of the parent melanoma cell line. Chromosome analyses, using the parentine fluorescence banding technique, failed to localize the suppressive effect to a specific chromosome. (18 refs)

- 79-1053 Human Peripheral Null Lymphocytes: Ultrastructural Aspects of the "K" Cell Effect Against a Melanoma Target Cell.** (Eng) Cesarini, J. P. (Laboratoire de Recherche sur les Tumeurs de la Peau Humaine, Fondation A. de Rothschild, 29 rue Manin, 75019 Paris, France); Roubin, R.; Kalden, J. R.; Peter, H. H. *Biomedicine* 28(4): 219-225; 1978.

The Fc-receptor-bearing killer (K) cells in a human null cell lymphocyte fraction, which exhibited cytotoxic activity against antibody-sensitized human melanoma target cells, was characterized ultrastructurally. The homogeneous population of mononuclear cells found in close contact with the target cells was 8-10 μ m in diameter, with an irregular nu-

cleus, discrete rough endoplasmic reticulum, isolated ribosomes, a large cytoplasm, and a ruffling membrane in close contact with the tumor cell. (30 refs)

- 79-1054 Association of Melanoma Tumor Antigen Activity with β_2 -Microglobulin.** (Eng) Malley, A. (Dept. Immune Diseases, Oregon Regional Primate Res. Center, Beaverton, OR, 97005); Burger, D. R.; Vandembark, A. A.; Frikke, M.; Finke, P.; Begley, D.; Acott, K.; Black, J.; Vetto, R. M. *Cancer Res* 39(2, part 2): 619-623; 1979.

The relationship between β_2 -microglobulin (β_2m) and melanoma tumor antigen (MTA) present in KCl extracts of freshly excised tumor tissue was evaluated. Most MTA activity present in the melanoma extracts bound to a Sepharose-anti- β_2m adsorbent. This association was not due to the presence of histocompatibility locus antigens (HLA) in the extract. Removal of HLA antigens from the KCl extracts by KBr flotation did not reduce the MTA activity of the extracts, and the MTA activity still appeared to be associated with β_2m . The complete blocking of MTA activity by pre-treating the anti- β_2m adsorbent with β_2m and the lack of detectable MTA binding to a Sepharose anti-normal human serum adsorbent demonstrated the specificity of the binding of MTA to the anti- β_2m adsorbent. The data suggest that β_2m provides the means for MTA and other proteins to become associated with lymphocyte cell surfaces. (16 refs)

- 79-1055 Malignant Angioendothelioma--Effect of Immunotherapy with *Corynebacterium parvum*.** (Eng) Tan, S. G. (Dept. Dermatology, General Infirmary Leeds, Leeds, England); Cotterill, J. A.; Roberts, M. M.; Cunliffe, W. J. *Acta Derm Venereol (Stockh)* 58(6): 551-553; 1978.

A 76-yr-old man with malignant angioendothelioma of the scalp was given adjunct *Corynebacterium parvum* intralesional immunotherapy. Although the patient died before the effect of the *C. parvum* could be assessed adequately, compared with uninjected tumor sites, sections of the injected sites showed a much greater degree of necrosis with an associated neutrophil polymorph infiltrate, but no lymphocytic reaction. (8 refs)

- 79-1056 Enhancement of Resistance to Murine Osteogenic Sarcoma In Vivo by an Extract of *Brucella abortus* (Bru-Pel): Association with Activation of Reticuloendothelial System Macrophages.** (Eng) Glasgow, L. A. (Dept. Pediatrics, Univ. Utah Coll. Medicine, Salt Lake City, UT, 84132); Crane, J. L.; Schleupner, C. J.; Kern, E. R.; Youngner, J. S.; Feingold, D. S. *Infect Immun* 23(1): 19-26; 1979.

The capacity of an aqueous-ether-extracted residue of *Brucella abortus* (Bru-Pel) to enhance host resistance to the development of a transplantable osteogenic sarcoma (OGS) was investigated along with its antitumor and antiviral activity. C57Bl/6J mice were inoculated with Bru-Pel (1,000 μ g ip) either 14 days before, immediately preceding (day 0), or 3 or 7 days after ip inoculation with 10^5 OGS cells. After 2 mo of observation, the mortality of tumor-inoculated mice was significantly reduced when Bru-Pel was given on day -14, 0, or +3, but not on day +7. *Corynebacterium parvum* (1,400 μ g ip) was also effective when given on day -14 or 0, but two interferon inducers failed to give any protection against tumor development. Peritoneal macrophages harvested from mice that had received Bru-Pel were cytotoxic for OGS cells in vitro, limited the replication of vaccinia virus in cell cultures, and demonstrated enhanced emissivity of chemiluminescence during phagocytosis of zymosan particles of *Candida albicans*. Bru-Pel-activated macrophages were also cytotoxic for syngeneic mouse embryo fibroblasts; the reason for this effect is not known. Bru-Pel-treated mice had a markedly enhanced resistance to mortality from *Listeria monocytogenes*. These observations support the hypothesis that Bru-Pel shares a number of characteristics with recognized immunomodulating agents and that one mechanism by which it modulates host resistance is activation of macrophages of the reticuloendothelial system. (32 refs)

- 79-1057 Suppressive Versus Augmenting Effect of the Same Pretreatment Regimen in Two Murine Tumor Systems with Distinct Effector Mechanisms.** (Eng) Fufiwaru, H. (Inst. Cancer Res., Osaka Univ. Medical Sch., Fukushima 1-1-50, Fukushima-ku, Osaka 533, Japan); Hamaoka, T.; Kitagawa, M. *Gann* 69(6): 793-803; 1978.

The effect of presensitization with x-irradiated tumor cells on the development of the host's immune resistance against the tumor-associated transplantation antigens was investigated using the X5563 plasmacytoma and MM102 mammary tumor systems (both of C3H/He origin) in C3H/He mice. The acquisition of T-cell-mediated immune resistance against the X5563 plasmacytoma was suppressed in syngeneic mice pre-treated with x-irradiated X5563 cells. The development of an immune cell population was inhibited by serum factors but not by suppressor cells. When the serum factor mediating this tumor-specific suppression was fractionated on a Sephadex G-200 column, the suppressive activity was found in the albumin-corresponding fraction and was free of IgG and IgM. In the MM102 mammary tumor system, in which immune resistance is mediated solely by tumor-specific antibody, pre-treatment with x-irradiated MM102 cells eventually augmented the induction of anti-tumor immunity without any enhancement of tumor growth. The results indicate that tumor antigens given by the same presensitization regimen have different effects on the distinct effector mechanisms of two different tumor systems of the same syngeneic mice. (29 refs)

79-1058 Granuloerythropoietic Colonies in Human Bone Marrow, Peripheral Blood, and Cord Blood.

(Eng) Fauser, A. A. (Ontario Cancer Inst., 500 Sherbourne St., Toronto, Ontario M4X 1K9, Canada); Messner, H. A. *Blood* 52(6): 1243-1248; 1978.

Conditions supporting the growth of granuloerythropoietic colonies [colony-forming unit (CFU)-G/E] in specimens of human bone marrow, peripheral blood, and cord blood are reported. Colony growth is promoted by media conditioned by WBC in the presence of phytohemagglutinin and by the addition of erythropoietin to the cultures on days 4 or 5. Sedimentation velocity profiles suggest that the colonies originate from single cells (CFU-G/E) rather than from doublets or clumps. This hypothesis is supported by cocultivation of male and female specimens. Cells in the granuloerythrocytic colonies that developed in these mixing experiments were either uniformly female by Y-chromatin analysis or they contained Y-chromatin bodies in both the granulocytic and erythroid cells. (14 refs)

79-1059 A Nude Mouse with Enlarged Thymic Rudiment. (Eng) Imamura, N. (Dept. Pathology,

Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi 1-2-3, Hiroshima 734, Japan); Yokoro, K. *Gann* 69(6): 859-860; 1978.

The immunohistology of an enlarged thymic rudiment in a nude mouse was studied. The animal was killed 3 mo after sc inoculation with chemically-induced rat leukemic cells. No take of the leukemic transplant was evident at autopsy, and there was no ectopic thymus around the neck of the mouse. Twenty-five percent of the animal's spleen cells expressed Thy-1.2 antigen, compared with <7% of most nude mice. The thymus-like tissue showed no lymphocyte proliferation, and it was histologically embryonal. The thymus-dependent lymphoid tissue showed an increased small lymphocyte population relative to other nude mice. The data suggest that the embryonal thymus possesses the ability to induce T-cell differentiation. (5 refs)

79-1060 Thymic Deficiency in Down's Syndrome. (Eng)

Levin, S. (John Askin Labs., Pediatric Res. Dept., Kaplan Hosp., Rehovot, Israel); Schlesinger, M.; Handzel, Z.; Hahn, T.; Altman, Y.; Czernobilsky, B.; Boss, J. *Pediatrics* 63(1): 80-87; 1979.

Histologic studies were made of the thymuses of 12 infants with Down's syndrome (DS) and 12 infants without DS who were matched for age and, as closely as possible, for cause of death and length and nature of terminal illness. Immunologic studies were made of the blood of 20 infants and children with DS (age range 1 day to 10 yr) and of the cord blood of 8 newborns with DS. Results of some immunologic studies of 12 adult patients with DS are also included. The

mean wt of the DS thymuses was 3.3 g vs 5.6 g for control thymuses. Almost every DS thymus was histologically abnormal, demonstrating lymphocyte depletion, diminution of the cortex, and loss of corticomedullary demarcation, changes resembling thymic involution. In addition, Hassall's corpuscles were markedly enlarged, and some were surrounded by a sheath of lymphocytes. Immunologically, there was a significantly lower percentage of T cells in the peripheral blood of DS patients than in the blood of normal controls. The mean lymphocyte count of these patients was also lower than control values, but the differences were not statistically significant. Children and newborns with DS exhibited a markedly diminished response to phytohemagglutinin (PHA), but adults with DS did not show this decrease. PHA-stimulated immune interferon production and polyinosinic-polycytidylic acid-stimulated classic viral interferon production were also significantly diminished in patients with DS. The deficient cell-mediated immune system could explain some of the abnormal clinical findings in DS patients, such as increased respiratory infections and lymphatic leukemia. (42 refs)

79-1061 Influence of Inoculation Site on Development of the Lewis Lung Carcinoma and Suppressor Cell Activity in Syngeneic Mice. (Eng) Malave, I. (Dept. Experimental Medicine, Instituto Venezolano de Investigaciones Cientificas, Apartado 1827, Caracas 101, Venezuela); Blanca,

I.; Fuji, H. *J Natl Cancer Inst* 62(1): 83-88; 1979.

The growth of the Lewis lung carcinoma (3LL) was studied in syngeneic C57BL/6 mice inoculated sc with similar numbers of tumor cells in either the flank or the hind footpad (fp). After injection of small numbers of 3LL cells (10^3 or 10^4), the incidence of tumors was lower in the flank than in the fp. However, after a successful 3LL transplant, tumors in the flank progressed faster than those in the fp, as evidenced by the early metastatic dissemination to the lungs and the shorter survival of the hosts. Local adoptive transfer tests demonstrated the early appearance of suppressor cell activity in spleens from mice bearing tumors in the flank. Adult thymectomy as well as treatment with antithymocyte serum after the tumor transplant inhibited the growth of a flank tumor but did not modify significantly that of an fp tumor. Thus, variations in the site of an sc tumor implant resulted in differences in tumor development that appeared to depend on the characteristics of the immune response elicited by the inoculum. (34 refs)

79-1062 The Assessment of Antichymotrypsin in Cancer Monitoring. (Eng) Kelly, U. L. (Dept. Cancer Res., Univ. Leeds, Leeds LS2 9NL, England); Cooper, E. H.; Alexander, C.; Stone, J. *Biomedicine* 28(4): 209-215; 1978.

Serum levels of antichymotrypsin (ACT), antitrypsin (AT), and α_1 -acid glycoprotein (AGP) were compared in 680 samples taken from normal donors, cancer patients at various

stages of disease, and cancer patients apparently cured after tumor excision. In all invasive cancers, the median levels of these three acute-phase reactant proteins were increased over control values. According to preliminary data, the relative frequency distribution of ACT in early and advanced metastatic colorectal cancer and invasive bladder cancer was bimodal. The bladder cancer data suggested that the ACT level rises with an increasing tumor load. Longitudinal studies of patients who had undergone tumor excision revealed that after recovery from the surgery, ACT, in common with the other two proteins, was very stable until the development of a recurrence or metastases. Prostate and breast cancer patients placed on estrogen therapy showed a decrease in ACT after therapy initiation, partly due to tumor remission and partly due to a direct estrogen effect. The normal donors, unlike the cancer patients, had a normal distribution of ACT. This, plus the fact that the protein shows no phenotypic variation, indicates that ACT is a good candidate for inclusion in a multivariate system for tumor monitoring. (12 refs)

79-1063 Characterization of Murine Tumor-associated Antigens by the Micro-leukocyte Adherence Inhibition Assay. (Eng) Howell, J. H. (Dept. Surgical Oncology, Roswell Park Memorial Inst., Buffalo, NY, 14263); Russo, A. J.; Goldrosen, M. H. *Cancer Res* 39(2, part 1): 612-618; 1979.

The micro-leukocyte adherence inhibition (LAI) assay was used to monitor the solubilization and purification of tumor-specific antigens from a murine colonic adenocarcinoma (MCA-38) and from a spontaneous murine melanoma (B16), both syngeneic to C57BL/6J mice. Three extraction procedures were performed on the membrane preparations of the tumors: 1 M perchloric acid (PCA), 3 M KCl, and deoxycholate solubilization followed by brief papain treatment. The deoxycholate/papain extract was without activity in the LAI assay; however, significant recognition of the former two extracts was observed with peritoneal cells from tumor-bearing mice. The lack of appreciable activity in the detergent- and papain-solubilized material suggests that the antigen detected in the LAI assay is not similar to murine histocompatibility (H-2) antigens, since this solubilization procedure has previously provided excellent yields of H-2 antigens. Plasma membrane vesicles prepared from cultured tumor cells also

demonstrated specific antigenic activity. The PCA extract of MCA-38 tumor was fractionated on Bio-gel P-200 and on Sephacryl S-200, and the LAI reactivity was found in a fraction with a mol wt > 160,000. A rabbit antiserum to the 1 M PCA extract of MCA-38 tumor was prepared, and after solid state absorption with 1 M PCA extracts of C57BL/6J murine colon, liver, and kidney, no Ouchterlony immunoprecipitation activity was observed against the P-200 fraction containing the LAI reactivity. Immunoprecipitation was obtained with the PCA fraction with a mol wt of 45,000-158,000. This material is heat-stable, and it migrated as a β -protein in immunoelectrophoresis. These results suggest that the MCA-38 colon carcinoma contains a glycoprotein with some carcinoembryonic antigen-like properties, as well as a distinct specific tumor-associated antigen recognized in the LAI assay. (36 refs)

See also:

- *(Rev.): 79-0623, 79-0626, 79-0627, 79-0628, 79-0631, 79-0633.
- *(Chem.): 79-0664, 79-0671, 79-0738, 79-0799, 79-0825, 79-0830, 79-0832, 79-0875, 79-0876.
- *(Viral): 79-0982, 79-0983, 79-0985, 79-0991, 79-0993, 79-0994, 79-1001, 79-1007, 79-1008, 79-1014, 79-1017, 79-1029.
- *(Path.): 79-1073, 79-1101, 79-1106, 79-1130.
- *(Epid.-Biom.): 79-1143.

PATHOGENESIS

- 79-1064 Genetic Material and Cancer: Genetics of Cancer.** (Fre) Jami, J. (No affiliation given). *Lyon Med* 240(16): 280-282; 1978.

A brief description is given of hybridization studies in which normal and malignant (fibrosarcoma) mouse cells were crossed. The hybrid cell, which was malignant (produced tumors in mice), contained genetic information that was not present in the normal cell. Further studies using human cells are proposed. (no refs)

- 79-1065 Erythropoietin (Ep) Dose-Response Curves for Three Classes of Erythroid Progenitors in Normal Human Marrow and in Patients with Polycythemia Vera.** (Eng) Eaves, C. J. (Medical Biophysics Unit, British Columbia Cancer Res. Centre, 601 W. 10th Avenue, Vancouver B.C., Canada V5Z 1L3); Eaves, A. C. *Blood* 52(6): 1196-1210; 1978.

Three classes of normal human erythropoietic progenitor cells were studied with respect to their erythropoietin (Ep) sensitivity under various culture conditions. Dose-response curves extending from 0.001 to 10 units Ep/ml indicated that, under optimal conditions, the formation of very large erythroid colonies (or "bursts") [from primitive burst-forming units-erythroid (BFU-E)] required about 3-fold more Ep than that needed for small bursts from mature BFU-E and about 5-fold more Ep than that needed for the production of small erythroid clusters [from colony-forming units-erythroid (CFU-E)]. Removal of the adherent marrow cell fraction and/or omission of leukocyte-conditioned medium from the cultures resulted in failure to achieve maximum burst formation by primitive BFU-E. The effect was not as great on mature BFU-E and was minimal on CFU-E. Ep dose-response curves indicated two coexisting populations in polycythemia vera (PV): one with hyper-Ep-responsive cells and one with normal in vitro Ep sensitivity. There was a progressive increase in favor of the abnormal cells in the later, mature BFU-E and CFU-E compartments. The data suggest that RBC precursors show progressive changes in their response to Ep and other factors that affect burst formation in vitro. With regard to PV, there may be a growth advantage of the abnormally Ep-sensitive line proliferating in a low Ep environment. (23 refs)

- 79-1066 Relationship Between Serum Iron, Plasma Iron Disappearance Rate, and Plasma Iron Turnover in Various Hematologic Diseases.** (Jpn) Saito, H. (Radiology

Dept., Nagoya Univ. Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya 466, Japan). *Radioisotopes* 27(11): 656-658; 1978.

The relationship between serum iron, plasma iron disappearance rate (PIDR), and plasma iron turnover was determined for 26 patients with hematologic diseases, including aplastic anemia, hypoplastic anemia, hemolytic anemia, paroxysmal nocturnal hemoglobinuria, hereditary spherocytosis, and polycythemia vera. In general, when serum iron was increased, the PIDR was elevated, and when serum iron was decreased, the PIDR was low. In both situations, the plasma iron turnover was not affected. However, these situations did not hold for all the hematologic diseases, and exceptions are described. (6 refs)

- 79-1067 Feline Preleukemia: An Animal Model of Human Disease.** (Eng) Maggio, L. (Dept. Medicine, Sch. Veterinary Medicine, Univ. Pennsylvania, Philadelphia, PA); Hoffman, R.; Cotter, S. M.; Dainiak, N.; Mooney, S.; Maffei, L. A. *Yale J Biol Med* 51(4): 469-476; 1978.

A naturally occurring syndrome in domestic cats that resembles human preleukemia is described. Twelve cats (9 males, 3 females) were evaluated for lethargy, anorexia, and wt loss. Mucous membrane pallor was present in eight, fever in eight, and hepatosplenomegaly in six. All animals were anemic (mean hematocrit: 14.5%), and anemia was severe in four animals. Although macrocytosis without polychromasia was occasionally evident in the peripheral blood smear, normochromic, normocytic RBC morphology was the rule. Nucleated RBC precursors were observed in 10 animals. WBC abnormalities at presentation were confined to leukopenia with granulocytopenia. Only two cats were feline leukemia virus (FeLV)-negative at presentation. These two became viremic when they developed overt leukemia. Four of eight bone marrow aspirates showed mild to moderate lymphocytosis. The time interval from the development of anemia to the diagnosis of overt leukemia varied from 1 wk to 33 mo. The natural occurrence of this syndrome in this domestic animal population makes it a potential model of human preleukemia. (46 refs)

- 79-1068 Preleukemic Syndrome. Hematopoietic Dysplasia.** (Ita) Majolino, I. (Universita degli Studi, Pavia, Italy); Panizza, P.; Nalli, G.; Trpin, L.; Barosi, G.; Ascari, E. *Recent Prog Med (Roma)* 64(4): 404-445; 1978.

Studies and observations on hematopoietic dysplasia as

preleukemic syndromes are reviewed, and new cases are presented. Sideroblastic anemia was diagnosed in three men aged 64, 54 and 64 yr a few months before they developed leukemia. Paroxysmal nocturnal hemoglobinuria was diagnosed in a 34-yr-old man nearly 2 yr before he developed leukemia. Aplastic anemia preceded leukemia in a 16-yr-old man and a 67-yr-old woman. Refractory anemia was diagnosed in two women aged 23 and 72 yr and two men aged 55 and 65 yr before they developed leukemia. One of the two men was a radiologist. (180 refs)

- 79-1069 Childhood Leukemia Presenting as a Diaphyseal Radiolucency.** (Eng) Bos, G. D. (Section Orthopedic Surgery, Pritzker Sch. Medicine, Univ. Chicago, Box 421, 950 E. 59th St., Chicago, IL, 60637); Simon, M. A.; Spiegel, P. G.; Moohr, J. W. *Clin Orthop* (135): 66-68; 1978.

The case of a 41-mo-old boy with leukemia who presented with a symptomatic diaphyseal destructive lesion of the femur is reported. At presentation, pain in both thighs and pyrexia were the only symptoms. A bone scan showed increased uptake in one femur. Biopsy demonstrated numerous blast cells compatible with acute lymphocytic leukemia. (10 refs)

- 79-1070 Sister Chromatid Exchanges and Chromosomes in Chronic Myelogenous Leukemia and Cancer Families.** (Eng) Cheng, W. S. (Medicine Branch, NCI, Bethesda, MD, 20014); Mulvihill, J. J.; Greene, M. H.; Pickle, L. W.; Tsai, S.; Whang-Peng, J. *Int J Cancer* 23(1): 8-13; 1979.

Banded karyotypes and baseline frequencies of sister chromatid exchanges (SCE) were studied in blood lymphocytes from 96 individuals: 7 patients with chronic myelogenous leukemia (CML), 15 normal controls, and 5 "cancer families" comprising 12 cancer patients, 40 tumor-free blood relatives, and 22 spouses. The diseases in each family consisted of malignant melanoma, Epstein-Barr virus-associated malignancies and a birth defect syndrome, non-Hodgkin lymphoma and diverse carcinoma, Hodgkin's lymphoma and adenocarcinomas, and acute myelogenous leukemia. In addition to the presence of the Philadelphia chromosome in the patients with CML, karyotypic abnormalities, especially breaks and fragments, occurred in 29% of the cancer family members, but they were inconsistent and usually attributable to radiotherapy. Mean SCE values were normal in CML, but were low (by t-test) in the cancer family tumor patients combined ($p = 0.026$) and in their blood relatives. In the tumor patients, mean levels of SCE declined with increasing age ($p = 0.03$). After adjusting for this age effect, no significant differences remained among groups. In patients at high risk of cancer (ie, because they had CML or a strong family history of cancer), spontaneous SCE rates were not a marker of cancer risk. (27 refs)

- 79-1071 Bullous Pyoderma Gangrenosum and Acute Leukemia.** (Eng) Sheps, M. (Nurses' Residence, No. 202, 399 Bathurst St., Toronto, Ontario, Canada M5T 2S8); Shapero, H.; Ramsay, C. *Arch Dermatol* 114(12): 1842-1843; 1978.

Two episodes of bullous pyoderma gangrenosum (BPG) occurred in a 33-yr-old woman, one several months before evidence of leukemia appeared and one concurrently with acute myelogenous leukemia. A skin biopsy early in the second episode showed a panniculitis, with a predominance of polymorphonuclear WBC invading the fat septa. It is suspected that the first illness was acute leukemia and that the systemic steroids used to control the BPG also induced remission of the leukemia. (7 refs)

- 79-1072 Absence of Late-replicating X-Chromosome in a Female Patient with Acute Myeloid Leukemia and the 8;21 Translocation.** (Eng) Levan, G. (Dept. Genetics, Univ. Gothenburg, S-414 63 Gothenburg, Sweden); Mitelman, F. *J Natl Cancer Inst* 62(2): 273-275; 1979.

An attempt was made to determine the status of activity of the remaining X chromosome in women with acute myeloid leukemia (AML) characterized by the 8;21 translocation and the loss of one X chromosome. To study late DNA replication, a complete karyotype analysis plus continuous labeling autoradiography were performed on 19 cells of a 41-yr-old female AML patient. This was done during partial remission, when the bone marrow contained cells with both 45 and 46 chromosomes. In all XO cells analyzed, the single X was always early-replicating; ie, it was the active X chromosome. It is suggested that in patients housing AML with the 8;21 translocation, loss of the inactive X chromosome in women and the Y in men (which occurs in approx 50% of patients) entails selective advantage to the stemline. The most likely explanation for the absence of the late-replicating X chromosome in this study is that this chromosome was lost from a single cell and that the stemline population developed from this cell. (9 refs)

- 79-1073 Systemic Lupus Erythematosus and Malignant Histiocytosis (Letter to Editor).** (Eng) Fournie, G. J. (Laboratoire d'Immunopathologie Renale, Service de Nephrologie et d'Hemodialyse, C.H.U. Toulouse-Purpan, 31052 Toulouse, France); Conte, J. J.; Delsol, G.; Fabre, J.; Miguieres, J.; Jover, A. *Lancet* 2(8103): 1305-1306; 1978.

Malignant histiocytosis (MH) was diagnosed 9 mo after the onset of systemic lupus erythematosus in a 24-yr-old man who presented with polyarthralgia, fever, and facial erythema. No immunosuppressive therapy was given before the MH developed. However, the timing invites speculation about the induction of autoimmune disorders in association with malignancy and the induction of both diseases by the same etiological agent (virus?). (4 refs)

- 79-1074 14q+ Marker Chromosome in an EBV-Genome-Negative Lymph Node Without Signs of Malignancy in a Patient with EBV-Genome-Positive Nasopharyngeal Carcinoma.** (Eng) Mitelman, F. (Dept. Clinical Genetics, Lund Univ. Hosp., S-221 85 Lund, Sweden); Klein, G.; Andersson-Anvret, M.; Forsby, N.; Johansson, B. *Int J Cancer* 23(1): 32-36; 1979.

The occurrence of a 14q+ marker chromosome in the inguinal lymph node of a patient with an Epstein-Barr virus (EBV)-genome-positive nasopharyngeal carcinoma is reported. The inguinal lymph node showed no morphological evidence of malignant lymphoma and no sign of metastatic tumor growth from the nasopharyngeal carcinoma. The lymph node was negative for EBV-determined nuclear antigen. A biopsy specimen from the nasopharyngeal tumor was found to contain 28 EBV-genome equivalents per cell; the cervical lymph node contained 19 EBV-genome equivalents per cell, while the inguinal gland did not contain detectable amounts of EBV-DNA. Chromosome analysis of 61 cells from the inguinal lymph node demonstrated that the 14q+ marker chromosome was an 8:14 translocation. This indicates that chromosome aberrations may precede histological signs of malignancy. (32 refs)

- 79-1075 Mycosis Fungoides--An Unusual Association (Letter to Editor)?** (Eng) Fraser, N. G. (Dept. Dermatology, Aberdeen Royal Infirmary, Aberdeen, Scotland); Donald, D. *Clin Exp Dermatol* 3(4): 456; 1978.

The case report of a man (48 yr old) with mycosis fungoides who, 23 yr earlier, had been treated for malignant lymphoma of the axillary lymph nodes is summarized. Recent histological review of the surgically excised lymph node specimens indicated that pleomorphic histiocytic type malignant lymphoma was present in the nodes. Skin biopsy showed a pleomorphic lymphoid cell infiltrate in the upper dermis with exocytosis and Pautrier's microabscesses in the epidermis. Therefore, the clinical and histological features suggest that the patient had developed two separate and unrelated lymphomas. The association of two unrelated lymphomas in the same patient is uncommon and has not been previously reported in mycosis fungoides. (6 refs)

- 79-1076 A Case of Eccrine Adenoma--Histological, Histochemical, and Enzyme Histochemical Studies.** (Jpn) Takematsu, H. (Dept. Dermatology, Tohoku Univ. Sch. Medicine, Sendai 980, Japan); Kato, T. *Jpn J Clin Dermatol* 32(11): 947-951; 1978.

A case of eccrine ductal adenoma in a 60-yr-old woman is reported. Histologically, the tumor tissue showed an increased amount of glycogen-containing epithelium and it was PAS-positive. There was an increased level of succinic-malate

dehydrogenase, which is characteristic of eccrine ductal adenomas. (20 refs)

- 79-1077 Multiple Familial Spiradenoma, Cutaneous Cylindroma, and Trichoepithelioma.** (Spa) Mag-nin, P. H. (Catedra de Dermatologia, Universidad Nacional de Buenos Aires, Urquiza 609, Buenos Aires, Argentina); Duhm, G.; Casas, J. G. *Med Cutan Iber Lat Am* 5(3): 179-187; 1977.

Multiple spiroadenoma, cutaneous cylindroma, plus trichoepithelioma (TE) were found in two members of a family, and a third member had multiple TE (all women, aged 19, 54, and 57 yr). There is an autosomal dominant association between multiple TE and the two other tumors. (19 refs)

- 79-1078 Juvenile Thyroid Carcinoma.** (Ita) Manetta, A. (I Divisione Chirurgica, Ospedale S. Gennaro, Naples, Italy); Cali, C.; Cevoli, S.; Mainiero, P. *Rass Int Clin Ter* 58(12): 839-846; 1978.

The occurrence of juvenile thyroid carcinoma in a 15-yr-old girl is reported, and the epidemiology and etiology of these tumors are discussed. Two years before the thyroid carcinoma was diagnosed, the patient had undergone subtotal thyroidectomy for a parenchymatous and colloid-cystic goiter. She observed the growth of a tumor several months after the operation. She subsequently underwent a second partial thyroidectomy, and the tumor was diagnosed as a follicular adenocarcinoma. The patient's history was unremarkable, but the published literature shows that 30%-40% of patients with juvenile thyroid carcinoma have been irradiated in infancy. Rats treated with thiouracil were found to develop thyroid tumors, the size of which was smaller in males than in females. Thyroiditis, especially Hashimoto's disease, is considered as a precancerous condition. (22 refs)

- 79-1079 Hyperplasia of the Adrenal Medulla.** (Ita) Scorza, R. (Istituto di Semeiotica Chirurgica, Università di Milano, Milan, Italy); Odero, A.; Giordanengo, F. *Minerva Med* 69(55): 3785-3794; 1978.

Arterial hypertension due to focal hypertrophy and hyperplasia of the adrenal medulla was found in a 28-yr-old man. A very small adenoma of the cortex was also found in the gland. The hypertension recurred after subtotal adrenalectomy, and the lesion was diagnosed as pheochromocytoma. (40 refs)

- 79-1080 Certain Aspects of Pheochromocytoma.** (Dut) van den Broek, P. J. (Afdeling Nierziekten,

Academisch Ziekenhuis, Leiden, Netherlands); de Graeff, J. *Ned Tijdschr Geneesk* 122(46): 1795-1801; 1978.

The clinical and prognostic aspects of pheochromocytoma are described on the basis of 43 new cases. They included 23 men and 20 women aged 17-70 yr. The pheochromocytoma was localized in one adrenal gland in 30 cases, was bilateral in 3, and was extraadrenal in 10 cases (paraortic in 6, thoracic in 2, and localized in the hilus of the kidney in 2). The pheochromocytoma was malignant in two cases; both patients developed lung metastases; one 0.5 and one 6 yr after surgery. (34 refs)

79-1081 A Clinicopathologic Study of 56 Cases of Intraocular Medulloepitheliomas. (Eng) Broughton, W. L. (Dept. Ophthalmology, Natl. Naval Medical Center, Bethesda, MD); Zimmerman, L. E. *Am J Ophthalmol* 85(3): 407-418; 1978.

A clinicopathologic and follow-up study was undertaken of 56 patients with intraocular medulloepithelioma. The median age at the time of initial clinical manifestation was 3.8 yr, but the median age at the time of surgery and histopathologic diagnosis was 5 yr. Pain and poor vision were the predominant symptoms, and leukocoria and a mass in the iris, anterior chamber, or ciliary body were the most frequent signs. Sixty-six percent of the medulloepitheliomas were classified as malignant. All of these had undifferentiated areas resembling retinoblastoma; 22 of 37 showed invasion of uvea, cornea, or sclera; 10 had sarcomatous components; and 16 exhibited exceptional pleomorphism or mitotic activity, or both. Seventeen of the 37 malignant tumors were teratoid. The 19 benign tumors were generally smaller and often confined to the inner surface of the ciliary body, posterior chamber, and retrolental area. These tumors were composed of sheets and cords of medullary epithelium resembling that of the embryonic retina and ciliary epithelium. Enucleation was the most frequent surgical treatment, being performed in a total of 43 cases. A diagnostic iridectomy or iridocyclectomy was performed before enucleation on eight patients who had masses in the iris or ciliary body. The most important prognostic feature was extraocular extension, which was observed in 10 cases. All four deaths due to tumor metastasis were preceded by clinically obvious orbital spread. In four additional cases with orbital involvement, the patients were lost to follow-up. It is concluded that the prognosis is worse than the results of this study indicate, especially among patients with extraocular extension. (13 refs)

79-1082 Leiomyoma of the Ciliary Body. (Eng) Vogel, M. (Univ. Eye Hosp., Gosslerstr. 12, D-3400 Gottingen, W. Germany); Spitznas, M.; Waubke, T. N. *Albrecht Von Graefes Arch Klin Ophthalmol* 209(2): 89-98; 1978.

The clinical, histological and electron microscopic features

of a ciliary body leiomyoma removed from the right eye of a 55-yr-old woman are presented. The moderately vascularized, round, lens-shaped tumor was excised completely. The retinal pigment overlying it was partly degenerated, and there was no infiltration of the adjacent sclera. The histopathologic diagnosis was leiomyoma or schwannoma. The size and shape of the cells and nuclei were variable and irregular, as shown by electron microscopy. The surface of the cells was covered by a very thick basement membrane, and the vast extracellular space between adjacent cells was filled primarily with a homogeneous electron-translucent ground substance containing striated collagen fibrils and a network of loosely arranged, fine fibrils. The electron microscopic diagnosis was smooth muscle cell tumor, with further differentiation regarding the malignancy of the tumor being impossible at this level. The differential diagnosis among amelanotic malignant melanoma, schwannoma, and neurofibroma is discussed. (7 refs)

79-1083 Metastatic Adenocarcinoma to the Anterior Uvea and Increased Carcinoembryonic Antigen Levels. (Eng) Denslow, G. T. (Dept. Ophthalmology, Univ. Kentucky Medical Center, Lexington, KY); Kielar, R. A. *Am J Ophthalmol* 85(3): 363-367; 1978.

The case report a 47-yr-old man with chronic unilateral iridocyclitis with secondary glaucoma is presented. An increased plasma carcinoembryonic antigen level (100 nanograms/ml) ultimately led to the correct diagnosis of metastatic adenocarcinoma to the anterior uvea. Although extensive clinical studies failed to demonstrate the primary tumor site, the results of histochemical staining indicate that it was in the gastrointestinal tract. (17 refs)

79-1084 Malignant Hemangioendothelioma (Wilson Jones Type)--Two Autopsy Cases. (Jpn) Kitamura, K. (Dept. Dermatology, Keio Univ. Sch. Medicine, Tokyo 160, Japan). *Jpn J Clin Dermatol* 32(11): 923-930; 1978.

Two cases of Wilson Jones-type malignant hemangioendothelioma, one in an 83-yr-old woman and one in a 77-yr-old man, are reported. In the former, the tumor developed from a small purplish growth on the head that was treated with 250-350 rads 3x/wk (total dose, 15,500 rads). Three months later, pneumothorax developed in the left and then the right lung. The tumor metastasized to the cheeks, front of the ears, and neck lymph nodes. The patient died 1 yr after diagnosis. The second patient developed a small tumor on the forehead, then a tumor at the front of the ear; both were resected. A total radiation dose of 11,200 rads was then given. However, an increasing number of tumors appeared on the face, the head, and the external auditory canal. They were treated with 200 rads/day. Subclinical lateral invasion of the tissues continued, however, and pneumothorax developed in the right

lung. The patient died from bilateral pneumonia 10 yr after diagnosis. (16 refs)

- 79-1085 Apocrine Cystadenoma.** (Jpn) Takeoka, K. (Dept. Dermatology, Kyorin Univ. Sch. Medicine, Shinkawa, Mitaka-shi, Tokyo 181, Japan); Chujoh, T.; Ishibashi, A.; Tanaka, M. *Jpn J Clin Dermatol* 32(11): 959-962; 1978.

A pea-sized swelling in front of the right ear of a 32-yr-old woman was resected and examined histologically. It had the typical characteristics of apocrine cystadenoma; ie, it was diastase-negative, PAS-positive, and colloid iron-positive, and it had lipofuscin-containing pigment granules in the epithelium. The features of this tumor are compared with those of 10 literature cases. (20 refs)

- 79-1086 Pacinian Neurofibroma (Letter to Editor).** (Eng) Webb, J. N. (Pathology Dept., Western General Hosp., Crewe Road, Edinburgh EH4 2XU, Scotland). *Histopathology* 2(6): 461; 1978.

An ultrastructural study has recently established that Pacinian neurofibromas are of nerve-sheath origin. The cell of origin is almost certainly the perineural cell, but an origin from the Pacinian corpuscle or other sensory nerve endings probably derived from cellular elements of the perineural sheath has not been ruled out. However, origin from the latter would be very difficult to prove, because the tumor would obliterate their very fine terminal axons. (no refs)

- 79-1087 Computer Tomography for Tumors of the Left Atrium.** (Ger) Lackner, K. (Radiologische Klinik, Universität Bonn, 5300 Bonn-Venusberg, W. Germany); Heuser, L.; Friedmann, G.; Thurn, P. *ROEFO* 129(6): 735-739; 1978.

The use of computer tomography (CT) in the diagnosis of cardiac tumors is illustrated by the case reports of three patients with myxomas of the left atrium. All three tumors were shown by CT as hypodense space-occupying lesions; accurate locations of the lesions were given by CT also. CT is recommended for cases of suspected heart tumors; echocardiography may give additional information on the movement of stalked tumors or thrombi. (26 refs)

- 79-1088 Cardiac Fibrosarcoma with Bone Metastases.** (Eng) Naimark, A. (Dept. Radiology, Jewish General Hosp., Montreal, Quebec, Canada); Lander, P.; Casoff, J.; Doggett, R. *J Can Assoc Radiol* 29(4): 275-276; 1978.

The third case of cardiac fibrosarcoma with bone metastases is reported. The constellation of multiple lytic bone lesions in association with unremitting pulmonary edema in a patient (a 47-yr-old man) without preexisting heart disease suggested the correct diagnosis, which was substantiated by echocardiography. (8 refs)

- 79-1089 Superficial Basal Cell Carcinoma of 32 Years' Duration.** (Eng) LoBuono, P. (Long Branch, 147 Pavilion Ave., Long Branch, NJ, 07740); Albert, J. *J Med Soc NJ* 75(13): 929-930; 1978.

A superficial basal cell carcinoma (BCC) of 32 yr duration was found incidentally in a 72-yr-old woman hospitalized for an unrelated problem. During the years of its growth, three different physicians misdiagnosed the carcinoma as eczema. Superficial spreading BCC differs clinically from other types of BCC--it usually is found on the trunk, it rarely invades underlying structures, and it is chronic. (3 refs)

- 79-1090 Adenoid Basal Cell Epithelioma Involving a Finger.** (Eng) Enna, C. D. (Clinical Branch, U.S. Public Health Service Hosp., Carville, LA). *Hand* 10(3): 309-311; 1978.

A rare case of adenoid basal cell epithelioma of the finger occurred in an 87-yr-old man who presented with a diffusely erythematous "raw" lesion of the skin overlying the dorsal aspect of the middle phalanx of the left ring finger. The lesion had increased slowly in size for 3 yr, and it showed no evidence of cellular secretory activity. Diagnosis was made upon punch biopsy. (4 refs)

- 79-1091 Subungual Squamous Cell Carcinoma.** (Eng) Attiyeh, F. F. (Dept. Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021); Shah, J.; Booher, R. J.; Knapper, W. H. *JAMA* 241(3): 262-263; 1979.

The clinical findings, diagnosis, and therapy in 12 patients (10 men, 2 women, aged 36-80 yr, av 58 yr) presenting with subungual squamous cell carcinoma during a 27-yr period are presented, and the relevant literature is reviewed. Trauma or chronic paronychia were predisposing factors in five patients, and chronic radiation exposure or radiation therapy could have played an etiological role in another five patients. Disarticulation of the distal phalanx proved to be effective therapy in most patients. (19 refs)

- 79-1092 Multiple Bowen's Disease.** (Jpn) Ohyama, K. (Dept. Dermatology, Kumamoto Univ. Medical

Sch., 1-1-1 Honso, Kumamoto 860, Japan); Kuwahara, H.; Hamada, M. *Jpn J Clin Dermatol* 32(11): 931-938; 1978.

A 76-yr-old man was hospitalized with about 150 pea-sized to walnut-sized flat pigment moles and an egg-sized tumor in the groin. Examination of the resected groin tumor revealed Bowen's carcinoma with clumped cells and individual keratinized cells. Topical therapy with 5% 5-fluorouracil was discontinued after 10 days because of erosion of the surrounding tissues. There was no sign of metastasis at this stage. Four months later, a swelling occurred in both groins; the tumors enlarged rapidly, and the patient died from cachexia. The patient had no history of an association with arsenic. (69 refs)

79-1093 Acantholytic Squamous Cell Carcinoma Arising on Senile Keratosis. (Jpn) Kimura, K. (Div. Dermatology, Kagawa Prefectural Central Hosp., Takamatsu 760, Japan); Fujita, H. *Jpn J Clin Dermatol* 32(11): 953-958; 1978.

A brown-grey swelling on the right wrist of an 88-yr-old man was excised. Histologically, the tumor appeared to be an acantholytic squamous cell carcinoma (ASCC). There was no sign of regional lymph node involvement. The site was treated with 5-fluorouracil for 1 mo; it became eroded after 3 wk and formed epithelium after 4 wk. One year later, however, small pea-sized tumors appeared at the site. They also had typical ASCC cells. There were clumps of keratinized columnar cells, which seems to be typical of acantholysis. (31 refs)

79-1094 Epithelioid Sarcoma of Hand and Forearm. (Eng) Boyes, J. G. (1928 Randolph Rd., Charlotte, NC); Marroum, M. C. *Hand* 10(3): 302-305; 1978.

The case of a 49-yr-old woman with an epithelioid sarcoma of the hand and forearm is reported. This tumor, which has a high rate of recurrence or metastasis, occurs predominantly in male manual workers aged 20-50 yr. The lesion presents in the palm, forearm, or anterior tibial areas as an ulcerating subdermal induration or as a multinodular lesion attached to the fascia or tendon sheath. Extension occurs directly to the skin or through the lymphatics. Metastasis occurs by erosion and invasion of blood vessels to the lung lymphatics and parenchyma. (8 refs)

79-1095 Metastatic Carcinoma of the Skin--Clinicohistopathological Observations. (Jpn) Tamura, N. (Dept. Dermatology, Keio Univ. Sch. Medicine, Tokyo 160, Japan); Kitamura, K. *Jpn J Clin Dermatol* 32(11): 963-970; 1978.

Clinical and histological findings in 20 cases of metastatic skin cancer seen since 1940 are presented. The original sites

of 15 tumors were the breast (5), stomach (4), uterus (2), colon (1), rectum (1), upper jaw (1), and kidney (1); the origin of 5 was not known. There were 3 cases of differentiated adenocarcinoma, 5 cases of undifferentiated adenocarcinoma, 4 cases of squamous cell carcinoma, and 6 cases of scirrhous carcinoma, 1 case of undifferentiated carcinoma, and 1 case of renal carcinoma. Among the 13 patients for whom follow-up data were available, the av survival rate was 10.5 mo. Clinically, 9 cases developed a single skin metastasis and 11 developed multiple skin metastases. Generally, squamous cell carcinoma originated from the breast, uterus, and upper jaw and it metastasized near the original sites. On the other hand, digestive tract cancers metastasized to sites all over the body. (17 refs)

79-1096 Giant Melanin Granules in Vitiliginous Achromia with Malignant Melanoma. (Eng) Ortonne, J. P. (Clinique Dermatologique, Hôpital Edouard Herriot, F-69374 Lyon Cedex 2, France); Perrot, H. *Acta Derm Venereol (Stockh)* 58(6): 475-480; 1978.

Histological and ultrastructural examination of the normal and perilesional skin of a 68-yr-old woman with vitiliginous depigmentation associated with a metastatic malignant melanoma revealed the presence of giant melanin granules in keratinocytes and melanocytes. These pigment masses may be the remains of melanophagosomes in which the protein structure of the melanosomes had been destroyed. The numerous instances of melanosome autophagocytosis seen in the periphery of the achromic lesions appear to support this concept. (14 refs)

79-1097 Hand Metastasis from Melanoma: A Case Study. (Eng) Gelberman, R. H. (Div. Orthopaedic Surgery, Univ. California at San Diego, Univ. Hosp., 225 W. Dickinson St., San Diego, CA, 92103); Stewart, W. R.; Harrelson, J. M. *Clin Orthop* (136): 264-266; 1978.

The case of a 24-yr-old man with an early peripheral metastatic lesion from melanoma is presented. The patient presented with right thumb pain 4 yr following the removal of a pigmented lesion from his shoulder. Biopsy demonstrated cortical destruction and soft tissue invasion by malignant melanoma. The patient underwent disarticulation of the thumb, excision of the old scar from the shoulder, and excision of an sc forearm lesion. He developed right proximal humerus metastasis 5 mo later, and he currently has pulmonary and widespread osseous metastases. (22 refs)

79-1098 Placental Metastasis of Disseminated Malignant Melanoma. Report of One Case. (Por) Silveira, E. (Departamento de Clinica Medica, Universidade Estadual de Campinas, Rua Alberto de Salvo, 311, 13.100

Campinas, Sao Paulo, Brazil); de Oliveira Filho, J. A.; de Souza, S. A.; Favaro Neto, A. *J Bras Ginecol* 86(2): 39-42; 1978.

Ovarian and placental metastases of a malignant skin melanoma were found in a 34-yr-old woman during Cesarean section. The cells of the placental metastasis were found in the intervillous space. The baby is apparently normal; the lack of fetal involvement is explained by its immune defense. (10 refs)

79-1099 Basal Cell Epithelioma in a Chronic Leg Ulcer. (Eng) Burns, D. A. (Dept. Dermatology, Royal Free Hosp., Pond St., London NW3 2QG, England); Calnan, C. D. *Clin Exp Dermatol* 3(4): 443-445; 1978.

The case report of a 79-yr-old woman with a 20-yr history of leg ulceration plus basal cell epithelioma is presented. Biopsy of the elevated margin of the ulcer revealed basal cell epithelioma. Tissue from a scarred area adjacent to the ulcer and from the margin of the ulcer did not show any evidence of neoplasia. Constant irritation and chronic infection are the probable etiological factors initiating neoplastic change in stasis ulcers. However, the incidence of neoplastic change in the lesions is extremely low, compared with the numbers of long-standing leg ulcers encountered. Some cases may be missed because the appearance of the ulcer is not atypical. Biopsy of chronic stasis ulcers should be performed more frequently so that a potentially remediable situation is not neglected. (3 refs)

79-1100 Synovial Hemangioma of the Knee. Report of a Case. (Fre) Rogez, J. M. (Clinique orthopédique adulte et infantile, Hôpital Saint-Jacques, 44035 Nantes Cedex, France); Letenneur, J.; Triclot, P.; Mussini, M.; Bainvel, J. V. *J Chir (Paris)* 115(10): 545-549; 1978.

The occurrence of a synovial hemangioma of the knee, a rare benign tumor, in an 11-yr-old boy is reported. The tumor is practically always palpable and is seldom spread diffusely. Because there are few specific clinical signs, the tumor is difficult to diagnose. (22 refs)

79-1101 Chemotactic Responses of Tumor Cells to Products of Resorbing Bone. (Eng) Orr, W. (Dept. Pathology, Univ. Manitoba Health Sciences Centre, Winnipeg, Canada R3E 0Z3); Varani, J.; Gondek, M. D.; Ward, P. A.; Mundy, G. R. *Science* 203(4376): 176-179; 1979.

To explore possible mechanisms for the metastasis of malignant cells to bone, a model of tumor cell migration using Walker carcinosarcoma or malignant lymphoma cells was developed. Culture media from fetal rat long bones stimulat-

ed to undergo resorption by products of Walker carcinosarcoma cultures were tested for chemotactic activity toward tumor cells, using modified Boyden chemotaxis chambers. Media from bone cultures in which resorption had occurred attracted significantly more tumor cells ($p < 0.05$) into its membrane filters than media from untreated bones. Chemotactic activity was not detected in the supernatant fluids from devitalized bones, or in control media. Migration of tumor cells to resorbed bone media was independent of the humoral mediator of bone resorption. Bones stimulated to resorb by supernatant fluids from cultured tumor cells, parathyroid hormone, or prostaglandin E_1 all released factors that stimulated the movement of tumor cells into the membrane filters. EL-4 murine lymphoma was also attracted by media from resorbing bones. Like the Walker carcinosarcoma cells, the cells of this tumor responded to bone-derived factors regardless of the mediator of bone resorption. The findings suggest that bone contains a factor that is chemotactic for tumor cells and is released when bone is resorbed. (15 refs)

79-1102 Chondrosarcoma Developed in the Distal Phalangeal Bone of the Third Toe: A Case Report. (Eng) Miki, T. (711-18 Hikisho Nishi-machi, Osaka, Japan); Yamamuro, T.; Oka, M.; Urushidani, H.; Itokazu, M. *Clin Orthop* (136): 241-243; 1978.

A 38-yr-old woman developed a chondrosarcoma in the distal phalanx of the third toe 10 yr following fracture of the distal third and fourth toes. The toe had become enlarged 4 yr after the fracture but only became painful after a minor accident. The clinical and radiological findings suggested that the tumor may have been due to a long-term enchondroma or residual cartilaginous fracture callus that eventually underwent malignant transformation. (9 refs)

79-1103 Ewing's Sarcoma in a 13-Month-Old Boy. (Ger) Tiedjen, K. U. (Nuklearmedizinische Abteilung Elisabeth-Hospitals, 4630 Bochum, W. Germany). *ROEFO* 129(6): 798-800; 1978.

Ewing's sarcoma in a 13-mo-old boy is described. The first symptoms were pain and swelling of the lower leg. X-rays, femoral arteriography, scintigraphy (perfusion and whole-body) and, finally, biopsy were used to make the diagnosis. No evidence for metastasis has been found in the 2nd yr after therapy (amputation and polychemotherapy). (15 refs)

79-1104 An Ivory Vertebra: Monostotic Paget's Disease of Bone. (Eng) Harris, D. J. (Dept. Pathology, Princess Margaret Hosp., Univ. Toronto, Toronto, Ontario, Canada); Hons, C. B.; Fornasier, V. L. *Clin Orthop* (136): 173-175; 1978.

The case of a 30-yr-old woman with Paget's disease of the 12th thoracic vertebral body is presented. The vertebral body was uniformly radiodense but had a normal outline, indicative of ivory vertebra. Metastatic radiological survey and scintigraphic examination confirmed that the patient had monostotic involvement. (15 refs)

- 79-1105 Chondromyxoid Fibroma of Lumbar Spine.** (Eng) Mayer, B. S. (Dept. Radiology, Univ. Oregon Health Sciences Center, Veterans Admin. Hosp., Portland, OR). *J Can Assoc Radiol* 29(4): 271-272; 1978.

The first occurrence of chondromyxoid fibroma in the lumbar spine is reported. The patient, a 23-yr-old man, was referred following abnormal preemployment films of the area. Radiography revealed a well-circumscribed, expanding, cystic lesion in the spinous process of the second lumbar vertebra with no involvement of the pedicles. A thick sclerotic rim and some scalloping of the inner margins were seen. (6 refs)

- 79-1106 Suppression of Malignancy in Human Lung Cancer (A549/8) x Mouse Fibroblast (3T3-4E) Somatic Cell Hybrids.** (Eng) Carney, D. N. (NCI-Veterans Admin. Medical Oncology Branch, 50 Irving St., N.W., Ward 2CN, Room C104, Washington, DC, 20422); Edgell, C. J.; Gazdar, A. F.; Minna, J. D. *J Natl Cancer Inst* 62(2): 411-415; 1979.

The highly tumorigenic human bronchioloalveolar lung cancer cell line A549/8 and the nontumorigenic mouse fibroblast line 3T3-4E were fused through the use of polyethylene glycol 1000 and analyzed after 40-50 generations for tumorigenicity, growth in agarose, and for 20/23 human chromosomes by isoenzyme markers. A549/8 is tumorigenic in nude (nu/nu) mice, forms colonies in agarose, and is not contact-inhibited; 3T3-43 exhibits the opposite traits. Isoenzyme analysis revealed preferential segregation of human chromosomes and retention of mouse chromosomes; however, each of the 20 human chromosomes assayed was represented in at least some of the 14 hybrid clones. All 14 independent hybrid clones tested in 85 nude (nu/nu) mice by sc inoculation were nontumorigenic, indicating that the malignancy of the lung cancer cells behaved as a recessive trait. Six hybrid clones formed colonies on agarose at efficiency rates of 1%-4%, but the remainder formed no clones. These phenotypes were discordant with all human isoenzymes tested, and agarose clonability could not be related to specific human chromosomes. The nontumorigenicity of the hybrids cannot be explained by the absence of a single copy of the 20 chromosomes analyzed, but gene dosage may play a role. (36 refs)

- 79-1107 Salmonella Infection Complicating Bronchoalveolar Carcinoma.** (Eng) Safirstein, B. H. (Dept.

Pulmonary Medicine, Saint Michael's Medical Center, Newark, NJ); Ramirez, E.; Dhakhwa, R. B.; Garfield, G. *J Med Soc NJ* 75(13): 921-923; 1978.

The rare association of alveolar cell carcinoma with secondary salmonella infection, which occurred in a 27-yr-old man, is documented. The patient presented with a 3-day history of purulent yellow sputum, cough, and fever. The report also underlines the difficulty in isolating salmonella organisms from blood, sputum, and bronchoscopic washings, despite continued clinical infection. The diagnosis of both conditions was established following open lung biopsy. (7 refs)

- 79-1108 Clear-Cell Carcinoma of the Lung Metastatic to the Hamate: A Case Report.** (Eng) Nissenbaum, M. (Hand Rehabilitation Center, Ltd., 243 S. 10th St., Philadelphia, PA, 19107); Kutz, J. E.; Lister, G. D. *Clin Orthop* (134): 293-296; 1978.

The case of a 46-yr-old man with clear-cell lung carcinoma metastatic to the hamate is presented. The symptoms simulated sympathetic dystrophy, and diagnosis was delayed because of the late appearance of radiographic changes over 6 mo after symptoms appeared. Early bone scanning in patients with chronic pain may provide useful information prior to the appearance of x-ray changes. (16 refs)

- 79-1109 Glomerulonephritis as a Prodromal Symptom of Lung Cancer.** (Fre) Unger, J. (Service de Medecine, Hopital Saint-Pierre, Universite Libre de Bruxelles, 322 Rue Haute, B 1000 Brussels, Belgium); Mockel, J.; Devroede, C.; Paduart, P.; Rutsaert, J. *Nouv Presse Med* 7(43): 3937; 1978.

A case of epimembranous glomerulonephritis occurred in a 59-yr-old man who, 10 mo later, was found to have lung cancer. The patient died 5 mo later of metastases from the undifferentiated epidermoid carcinoma. Bronchogenic cancer is the visceral solid tumor most likely to be associated with epimembranous glomerulonephritis. (3 refs)

- 79-1110 Asbestosis. A Clinical Material.** (Nor) Melbostad, E. (Lungeavdelingen, Rikshospitalet, Stockholm, Norway). *Tidsskr Nor Laegeforen* 98(31): 1561-1563; 1978.

Asbestosis was diagnosed in 10 patients (9 men, 1 woman, aged 41-71 yr) who had been exposed to asbestos occupationally for 1-41 yr (av 21 yr). All patients had lung fibrosis, eight had pleural reaction, and three of them had calcified plaques. (13 refs)

- 79-1111 A Case of Primary Germ Cell Tumor of the Posterior Mediastinum with Features of Endodermal Sinus Tumor.** (Jpn) Kobayashi, M. (Dept. Surgery, Shimane Prefectural Central Hosp., Shimane, Japan); Fujino, M.; Yumoto, T. *Jpn J Thorac Surg* 131(12): 942-945; 1978.

The case of a 63-yr-old man with posterior mediastinal germ cell tumor having features of an endodermal sinus tumor is presented. Histologically, the neoplasm contained communicating cavities, lined by cuboidal or flattened cells, and papillary structures. Cylindrical epithelial structures were located around the vessels, and in cross section these structures vaguely resembled immature glomeruli. Although most other similar tumors reported in the literature were fatal, this patient has been in good health for 5 yr following surgery. Postoperatively, he received 9,000 rads to the posterior mediastinum. (9 refs)

- 79-1112 Leiomyosarcoma of the Thorax.** (Eng) Carlson, D. H. (Dept. Radiology, Newton-Wellesley Hosp., Newton Lower Falls, MA, 02162); Hanelin, J. *J Can Assoc Radiol* 29(4): 221-224; 1978.

Three cases of leiomyosarcoma of the thorax are presented: an endobronchial lesion presenting with atelectasis, a parenchymal lesion presenting as a mass, and a rare extrapleural lesion arising in the chest wall. All three patients were men (aged 34, 65, and 71 yr), and three-fourths of the literature cases are in men. Two of the patients were admitted for evaluation of abnormalities seen on routine chest radiographs. The lesions are very aggressive, and all three patients died during their first postoperative year with metastatic disease. (20 refs)

- 79-1113 Carcinoma of the Antethoracic Skin Graft Esophagus.** (Eng) Kormano, M. (Dept. Diagnostic Radiology, Univ. Hosp., SF-20520 Turku 52, Finland); Yrjana, J. *ROEFO* 129(6): 789-790; 1978.

An epidermoid carcinoma developed at the upper anastomosis of a reconstructed esophagus in a 70-yr-old woman 51 yr after the operation (for lye stricture of the esophagus). A histologic diagnosis of squamous cell carcinoma of the antethoracic skin graft was made. The etiology may be chronic irritation, since many carcinomas are related to persistent fistula. In this patient, no fistula could be demonstrated until late in the course of the disease. Contrast radiology is limited in evaluating the nature of irregularities of the esophageal wall. (9 refs)

- 79-1114 Free Intestinal Transplantation in Cervical Esophageal Carcinoma.** (Ger) Keminger, K. (I. Chi-

urgische Universitätsklinik, Alser Strasse 4, A-1097 Vienna, Austria). *Acta Chir Austriaca* 10(3): 60-66; 1978.

Ten years after replacement of a lye-damaged esophagus by a retrosternal colon segment, a 55-yr-old woman experienced difficulty in swallowing. A pavement epithelial carcinoma at the anastomosis was diagnosed by biopsy. The defect was repaired with a free-intestinal transplant. Swallowing difficulty recurred 6 mo later. Carcinoma was found deep in the neck muscles. (5 refs)

- 79-1115 Directed Cytology of the Esophagus and Stomach. A Comparison of 3 Rapid Collection Methods.** (Eng) Graham, D. Y. (Dept. Medicine, Baylor Coll. Medicine, Houston, TX, 77030); Spjut, H. J.; Estrada, R. G. *Gastrointest Endosc* 24(6): 277-280; 1978.

Three methods for collecting cytological specimens from the esophagus and stomach without prolonging the endoscopic procedure are described. One is brush cytology, and two new methods make use of the aspiration channel of Olympus endoscopes. The new methods include aspiration of exfoliated cells directly from the surface of lesions, and aspiration of material remaining within the biopsy channel after brushing and/or forceps biopsies. Salvage of material remaining within the channel provides a useful and rapid method of obtaining specimens. (13 refs)

- 79-1116 A Case of Peutz-Jeghers Syndrome.** (Pol) Szklanny, J. (Klinika Chirurgii Ogólnej, Instytut Chirurgii AM, Lodz, Poland); Zimnicki, Z.; Wasiak, J.; Modzelewski, B. *Pol Przegl Chir* 50(8): 703-705; 1978.

A case of Peutz-Jeghers syndrome with gastric polyp was diagnosed in a 25-yr-old woman who underwent surgery for intussusception of the small intestine. (10 refs)

- 79-1117 An Evaluation of Gastric Biopsy in the Diagnosis of Gastric Cancer.** (Eng) Sancho-Poch, F. J. (Dept. Gastroenterology, Hosp. Sant Cruz y San Pablo, Barcelona 25, Spain); Balanzo, J.; Ocana, J.; Presa, E.; Sala-Cladera, E.; Cusso, X.; Vilardell, F. *Gastrointest Endosc* 24(6): 281-282; 1978.

The yield of endoscopic biopsy was assessed in a consecutive series of 174 gastric cancer patients seen during 1974-1975. A correct endoscopic diagnosis was made in 157 patients, and a histological diagnosis of malignancy was obtained by endoscopic biopsy in 163 patients. Plots of the number of positive biopsy fragments against the total number of fragments secured in each case, showed that all cases in which more than eight biopsies had been carried out included at least one positive for malignancy. Probability analysis showed that

when eight fragments were taken, there was a > 99% chance of a correct diagnosis in at least one. (12 refs)

- 79-1118 Gastric Polyps and Precancerous Mucosal Changes After Partial Gastrectomy.** (Eng) Janunger, K. G. (Dept. Surgery, Univ. Hosp., Umea, Sweden); Domellof, L. *Acta Chir Scand* 144(5): 293-298; 1978.

The incidence of gastric polyps among patients who had previously undergone a Billroth I (108 patients) or Billroth II (228 patients) procedure was compared with that among 407 nonoperated controls. Among the partial gastrectomy patients, 3.6% had stump carcinoma and 8.9% had gastric polyps (28 sessile polyps and 2 pedunculated polyps). The incidence of gastric polyps in the nonoperated controls was 4.9% (18 sessile and 2 pedunculated) and the age and sex distributions were similar to those in the gastrectomy group. Repeated endoscopic check-ups were performed in 57.4% of the gastrectomy patients. The diagnostic accuracy with regard to malignancy was not entirely satisfactory. Histological examination of the surgical specimen from one of four patients with precancerous changes showed a macroscopically invisible early carcinoma. Follow-up examinations disclosed carcinoma in 3 patients and precancerous changes or adenoma in 2 patients with sessile polyps. Careful reexamination of all patients with precancerous changes and gastric polyps is recommended. (31 refs)

- 79-1119 Primary Intestinal Localization of Hodgkin's Disease. A Case Initially Diagnosed as a Benign Eosinophilic Granuloma of the Small Intestine.** (Fre) Graveleau, P. (Service de Medecine Interne, Centre Medico-Chirurgical Foch, F 92151 Suresnes, France); Perol, R.; Mornet, P.; Morin, M. *Nouv Presse Med* 7(43): 3909-3911; 1978.

The case of a 49-yr-old woman with Hodgkin's disease confined to the small intestine and mesenteric nodes for 3 yr is reported. The intestine was resected in three separate interventions. The original diagnosis of eosinophilic granuloma was changed to Hodgkin's disease only when the patient was terminal and abdominal lymph node biopsies revealed Sternberg cells. (12 refs)

- 79-1120 Incidence of Polyps of the Large Intestine in General Hospitals. Study of 2,783 Consecutive Autopsies.** (Por) Aparecido Assiz, L. (Serv. de Gastroenterol. Cir., Hosp. do Servidor Publ. Estadual Francisco Morato de Oliveira, Sao Paulo, Brazil); Habr-Gama, A.; Claudio Godoy, A.; Ferrao, S.; Mattosinho Franca, L. C.; Goffi, F. S. *AMB: Rev Assoc Med Bras* 24(7): 251-252; 1978.

The incidence of polyps of the large intestine was studied in 2,783 consecutive autopsies performed during a 12-yr period.

The incidence of polyps in the large intestine was 91/2,783 (3.2%); 53 were found in men, 38 in women. Polyps were not found in the age group 0-20 yr (450 cases). The polyp was located in the cecum in 13 cases, in the ascending colon in 11, in the transverse colon in 10, in the descending colon in 16, and in the rectum and sigmoid in 28; the localization was not recorded in 13 cases. The polyp was associated with cancer in 18 cases; the cancer was localized in the sigmoid colon in 3 cases, in the stomach in 4, in the urinary bladder in 2, in the bile ducts in 3, in the bronchi in 2, in the liver in 2, and in the pancreas and prostate in 1 case each. (11 refs)

- 79-1121 Ectopic Production of ACTH by a Primary Adenocarcinoma of the Colon.** (Eng) Stambaugh, J. E. (1210 Brace Road, Cherry Hill, NJ, 08034); Redfield, E. S. *J Med Soc NJ* 75(13): 925-926; 1978.

The ectopic ACTH syndrome was found in a 72-yr-old man being treated for adenocarcinoma of the colon with hepatic metastasis. The diagnosis of the syndrome was suggested by the sudden development of severe hypokalemic alkalosis, profound weakness, and diabetes mellitus. It was confirmed by the finding of high serum and tumor levels of ACTH (185 picograms/ml and 2,350 picograms/g, respectively). This is the first documented instance of metastatic colonic adenocarcinoma producing the ectopic ACTH syndrome. (5 refs)

- 79-1122 The Place of Radiology in Tuberous Sclerosis (Bourneville's Disease).** (Ger) Teske, H. J. (Rontgendiagnostik-Abteilung, Universitätsklinikum der Gesamthochschule Essen, Hufelandstrasse 55, 4300 Essen 1, W. Germany). *ROEFO* 129(6): 770-777; 1978.

Two women (29 and 35 yr old) with an incomplete form of tuberous sclerosis, which was accompanied by bilateral renal tumors, are described. The incomplete form of the disease is difficult to diagnose, and angiography cannot always differentiate the accompanying tumors from malignant neoplasms. Both patients also showed typical changes in the fingers and toes as well as intracerebral calcification, and in one patient the lungs were affected. (131 refs)

- 79-1123 Double Hypernephroid Carcinomas of the Kidney.** (Ger) Weiland, H. (Radiologische Klinik, St. Vincenz-Krankenhaus Limburg, Auf dem Schafsberg, 6250 Limburg, W. Germany). *ROEFO* 129(6): 794-795; 1978.

A rare case of one-sided, double hypernephroid carcinoma of the kidney occurred in a 65-yr-old woman. Angiography showed two spherical, well-separated tumors (5 and 5.5 cm diameter) in the left kidney. The vessels of both tumors had the criteria of malignancy. The final diagnosis was based on histological findings. (3 refs)

- 79-1124 Ultrastructural Features in Normal and Hyperplastic Postmenopausal Endometrium.** (Eng) Deligdisch, L. (Mount Sinai Hosp., Fifth Ave. and 100th St., New York, NY, 10029); Yedwab, G.; Persitz, A.; David, M. P. *Acta Obstet Gynecol Scand* 57(5): 439-452; 1978.

The ultrastructural features of samples of normal and hyperplastic postmenopausal endometrium (PMEM) were compared. Of the total seven samples, four were diagnosed as adenomatous hyperplasia (2 of which were atypical) and 3 as normal PMEM. The most striking ultrastructural features of the hyperplastic endometrium were numerous nucleoli, deep nuclear membrane infoldings, an increased nucleocytoplasmic ratio, a prominent and enlarged rough endoplasmic reticulum closely associated with mitochondria and the nuclear membrane, abundant free ribosomes, and marked network microfilaments. In the two cases of atypical adenomatous hyperplasia, the protruded intraglandular proliferating epithelial cells exhibited more atypical features than the epithelial cells of the glandular lining, suggesting a more advanced degree of anaplastic change. The characteristic features of the normal PMEM were a paucity and random distribution of the cytoplasmic organelles and the presence of large cytoplasmic vacuoles and short, blunt microvilli. Secretory vacuoles opening into the lumen of the gland were found in one case of cystic atrophy of a normal PMEM. Collagenization was found in the stroma of both groups, although predominantly in the normal PMEM. In two cases of adenomatous hyperplasia, stromal cells with a vacuolar cytoplasm were found. The significance of these findings, as related to their importance as precursor stages of endometrial cancer (adenomatous and atypical adenomatous hyperplasia), as involutional manifestations (normal PMEM), and as related to the absence of cyclic activity (both groups) is briefly discussed. (11 refs)

- 79-1125 Classification and Stages of Carcinoma of the Uterine Cervix.** (Ita) Ferraris, G. (II Clinica Ostetrica e Ginecologica, Università di Torino, Via Ventimiglia, 3, Turin, Italy). *Minerva Med* 69(54): 3679-3686; 1978.

The 1976 F.I.G.O. (International Federation of Gynecology and Obstetrics) classification of carcinoma of the uterine cervix is presented. Carcinoma in situ and intraepithelial carcinoma are classified as Stage 0. In Stage I, the carcinoma is strictly limited to the cervix. Microinvasive carcinoma (initial stroma invasion) is classified as Stage IA and all other cases of Stage I as IB. In Stage II, the carcinoma is extended to the vagina but not to its inferior third nor to the pelvic wall. Unlike Stage IIB, there is no parametrial involvement in IIA. Involvement of the pelvic wall is the criterion for Stage III. Invasion of the vesical or rectal mucosa is seen in Stage IV. (no refs)

- 79-1126 The Significance of Lymphography for the Prognosis of Cervical Carcinoma.** (Ger) Schon-

dorf, N. (Universitäts-Frauenklinik, 6650 Homburg Saar, W. Germany); Amengual, M.; Dietz, R. *ROEFO* 129(6): 778-781; 1978.

The lymphograms (LG's) of 92 cervical carcinoma patients were compared with the histological findings in 45 of these patients. Histology confirmed the LG findings in 36 cases; the LG's were false-positive in 5 cases and false-negative in 4. During a 3- to 5-yr follow-up, the carcinoma progressed in 16/30 of the positive-LG patients vs 7/62 of those with normal LG's. The use of lymphography is recommended as a guide to the prognosis of patients with cervical carcinoma. (27 refs)

- 79-1127 Cervical Ectropion: Its Relationship with Carcinoma In Situ of the Uterine Cervix.** (Spa) Gaitan Galarza, V. (Laboratorio de Anatomia Patologica y Citologia Exfoliativa, LAPCE, Av. Oaxaca 96, Mexico 7, D.F., Mexico); Schulz Contreras, M.; Miranda Sanchez, A. *Patol Quir Citol Esfoliativa* 3(3): 143-151; 1977.

The relationship between cervical ectropion and carcinoma in situ of the uterine cervix was studied in 311 women (aged 15-80 yr) who underwent colposcopy, exfoliative cytology, and cervical biopsy. Ectropion was found in 141 cases (45%); all these patients were aged 15-60 yr; the incidence of ectropion was 100% in the age bracket 15-20 yr, 76% in the age bracket 21-30 yr, and lower in the higher age groups. The ectropion was periorificial in 118 cases, marginal in the others. Papillary ectropion was found in 125 cases, ectropion with regenerating epithelium in 10, polypoid ectropion in 4, and flat ectropion in 2. Intraepithelial carcinoma was found in 5/141 patients with ectropion, and in 2/170 patients without ectropion. The cytology revealed metaplasia in 87/141 patients with ectropion, and in 40/170 patients without ectropion. The findings indicate that metaplasia occurs preferably in ectropion, which is the most frequent premalignant lesion. (19 refs)

- 79-1128 Metamutation: A New Histogenetic Theory of Carcinoma In Situ of the Cervix.** (Eng) Duarte, E. (Rua Barao de Lucena, 95 Rio de Janeiro, RJ, Brazil). *J Bras Ginecol* 86(2): 19-28; 1978.

On the basis of histological observations of 418 patients with carcinoma in situ of the cervix from 1952 to 1977, a new histogenetic theory ("metamutation" theory) for the development of cervical carcinoma was conceived. According to this theory, the columnar cells of the endocervical epithelium undergo a metaplastic epidermoid transformation and after that a carcinomatous mutation, giving rise to carcinoma in situ of the cervix without going through dysplastic phases. (7 refs)

- 79-1129 Breast Biopsy at the Hospital dos Servidores do Estado (HSE). Results of 2,025 Examinations**

During the 1963-1972 Period. (Por) Toleda Piza, B. (Servico de Cirurgia Geral, Hospital dos Servidores do Estado, Rio de Janeiro, Brazil); Torres, E.; Lopes Chaves, L. C.; dos Santos, G. G.; Tanaka, E. *Rev Med HSE (Hosp Servidores Estado)* 29(4): 215-222; 1977.

Breast biopsy, performed in 2,025 women with mastopathy, revealed dysplasia in 1,010 cases, benign tumors in 344, malignant tumors in 329, various mastopathies in 288, and inflammation in 54. (5 refs)

79-1130 The Significance of Ferritin in Malignant Diseases. (Eng) Giler, S. (Dept. Surgery B, Rogoff-Wellcome Medical Res. Inst., Beilinson Medical Center, Petah Tikva, Israel); Moroz, C. *Biomedicine* 28(4): 203-206; 1978.

A subpopulation of circulating T lymphocytes bearing surface ferritin was recently found in patients with breast cancer and untreated Hodgkin's disease, but not in normal subjects or patients with benign breast disease. The appearance of this subpopulation in the circulation is an early manifestation of neoplastic disease, and its identification may provide a tool of potential diagnostic and prognostic importance in the management of breast cancer and Hodgkin's disease. (43 refs)

79-1131 Meconium Periorchitis. (Ger) Senff, A. (Institut für Pathologie der Universität Zurich, Universitätsspital, CH-8091 Zurich, Switzerland); Hedinger, C. *Z Kinderchir* 25(2): 125-135; 1978.

Two cases of meconium periorchitis are reported, as illustrations of the difficulty of diagnosing this condition. Both patients presented with palpable intrascrotal masses during the first 10 days of life. Both underwent complete removal of both testes because a malignant tumor was diagnosed. The correct diagnoses for both cases was reached only after further histological study. (27 refs)

See also:

*(Rev.): 79-0601, 79-0604, 79-0606, 79-0618, 79-0629, 79-0630, 79-0631, 79-0632, 79-0633, 79-0634, 79-0639, 79-0642, 79-0643, 79-0644, 79-0645.

*(Chem.): 79-0653, 79-0658, 79-0659, 79-0660, 79-0667, 79-0671, 79-0674, 79-0690, 79-0697, 79-0705, 79-0713, 79-0714, 79-0731, 79-0732, 79-0736, 79-0743, 79-0761, 79-0768, 79-0769, 79-0771, 79-0774, 79-0775, 79-0780, 79-0782, 79-0786, 79-0795, 79-0800, 79-0810, 79-0832, 79-0844, 79-0849, 79-0856, 79-0858, 79-0861, 79-0871, 79-0889, 79-0909, 79-0911, 79-0912, 79-0915, 79-0916, 79-0919, 79-0920, 79-0921, 79-0922, 79-0923.

*(Phys.): 79-0924, 79-0933, 79-0941, 79-0944, 79-0947.

*(Viral): 79-0987, 79-0995, 79-1016.

*(Immun.): 79-1044, 79-1046, 79-1052, 79-1058.

*(Epid.-Biom.): 79-1136, 79-1140, 79-1144, 79-1149, 79-1153, 79-1154, 79-1155, 79-1157, 79-1160, 79-1166, 79-1171.

- 79-1132 Sacrococcygeal Teratoma--Diagnosis and Therapy.** (Ger) Willital, G. H. (Kinderchirurgie, Chirurgische Univ.-Klinik Erlangen, Maximiliansplatz, 8520 Erlangen, W. Germany); Meier, H.; Schneider, H. *Z Kinderchir* 25(2): 113-125; 1978.

Data on sacrococcygeal teratomas are reviewed. The incidence is 1/30,000-40,000 births, and 75% of the patients are female. Only 9% have malignant tumors within the first 8 wk of life, but after that time the incidence of malignancy increases 50%-70%. (23 refs)

- 79-1133 Survey of Mortality among Employees Engaged in the Manufacture of Styrene and Polystyrene at the BASF Ludwigshafen Works.** (Eng) Frentzel-Beyme, R. (Deutsches Krebsforschungszentrum, Heidelberg, W. Germany); Thiess, A. M.; Wieland, R. *Scand J Work Environ Health* 4(Suppl. 2): 231-239; 1978.

The 1956-1976 mortality experience among persons employed at a West German styrene (SR)- and polystyrene-manufacturing plant for >1 mo since 1931 was surveyed. The cohort comprised 1,960 SR workers exposed for a total of 20,138 person-yr. There were 74 deaths, 12 of which were due to malignant neoplasms. The proportion of deaths due to malignant neoplasms was less in the cohort (14.9%) than in the entire population of West Germany (18.5%). Percentages of deaths due to neoplasms of the lymphatic and hematogenic systems were very similar in the two groups. When the cohort was subdivided into groups with 5-9, 10-14, or >15 yr of exposure, no increase in total mortality or mortality from malignant tumors occurred with increasing exposure time. Thus, it appears that prolonged exposure to SR is not a cancer hazard. (7 refs)

- 79-1134 Burkitt's Lymphoma of the Spinal Cord.** (Eng) Olumide, A. A. (Neurosurgery Unit, Dept. Surgery, University Coll. Hosp., Ibadan, Nigeria); Adeboye, A. *Trop Geogr Med* 30(2): 215-218; 1978.

The clinical pattern of Burkitt's lymphoma of the spinal cord seen in 20 patients during 1971-1976 is reported. Peak incidence was at 10-12 yr of age, and the major symptoms were paraplegia and various degrees of lower limb paresis, impaired sensation, and double incontinence. Hepatosplenomegaly was observed in 11 patients. The cerebrospinal fluid had elevated protein levels, and most patients were anemic on admission. (12 refs)

- 79-1135 Nasal Cancer Associated with Occupational Exposure to Organic Dust.** (Eng) Engzell, U. (Dept. Otorhinolaryngology, Huddinge Sjukhus, S-14185 Huddinge, Sweden); Englund, A.; Westerholm, P. *Acta Otolaryngol (Stockh)* 86(5/6): 437-442; 1978.

Records of the Swedish National Board of Health and Welfare were studied to determine whether the development of carcinoma of the nose and paranasal sinuses is related to occupational exposure to dust. Patients with nasal and paranasal sinus cancer were divided into one of two groups: 36 men and 10 women who presented with adenocarcinoma between 1961 and 1971 and 127 men and 85 women who presented with squamous cell or poorly differentiated carcinoma between 1965 and 1971. Fifty-three percent of the men in the first group had been employed as joiners, and at least 12 of these men had been cabinet makers. Three persons had been employed in the flour industry. The length of occupational exposure to dust among the nine joiners in whom this was established was 25 yr or more. No occupation predominated among the 62 men who responded to a questionnaire in the group with squamous cell or poorly differentiated carcinoma. The investigation shows that the bulk of men with adenocarcinoma of the nose and paranasal sinuses had been exposed to wood dust. (9 refs)

- 79-1136 Cancer Risk in Extensive Ulcerative Colitis.** (Eng) Kewenter, J. (Dept. Surgery III, Sahlgren's Hosp., S-413 45 Goteborg, Sweden); Ahlman, H.; Hulten, L. *Ann Surg* 188(6): 824-828; 1978.

Two hundred thirty-four patients who had developed extensive ulcerative colitis between 1951 and 1974 were followed until December 1975, and the cumulative risk of developing cancer of the large bowel was estimated. Fifteen patients with 17 large bowel carcinomas were found: 5 in the colon ascendens, 5 in the transversum, 3 in the sigmoid colon, and 4 in the rectum. The duration of ulcerative colitis in these patients was 7-44 yr. The expected number of colorectal carcinomas in a matched reference group was 0.49. The cumulative incidence of carcinoma 25 yr after the onset of colitis for the whole group of patients was 34%; it was 43% for those who developed the disease before 25 yr of age. These results suggest that elective surgery for patients with extensive colitis of 10-15 yr duration should be carefully considered. (19 refs)

- 79-1137 Clinical Features, Mortality and Survival of Patients with Asbestosis.** (Eng) Huuskonen, M. S. (Inst. Occupational Health, Haartmaninkatu 1, SF-00290

Helsinki 29, Finland). *Scand J Work Environ Health* 4(4): 265-274; 1978.

The clinical features, mortality, and survival rate of 202 patients (174 men, 28 women) diagnosed as having asbestosis between 1964 and 1976 at the Finnish Institute for Occupational Health were determined. Of the 202 patients, 133 had a clinical reexamination. Major characteristics included breathlessness in 118, persistent sputum in 95, crepitations in 77, and finger clubbing in 43. The underlying cause of death of the 62 patients who died before the study began were asbestosis (26), lung cancer (20), other malignancies (4), and other causes (12). Lung cancer was peripheral in 17 cases and central in 3. Peripheral cancers were located in the upper lobe in 11 cases and in the lower lobe in 6 cases. Nine of the lung cancer patients were insulators, 6 were asbestos quarry workers, 4 worked in a factory manufacturing asbestos cement products, and 1 was a carpenter who had been exposed indirectly. The number of deaths among the male patients was 56, compared to the expected number of 23.4 estimated from the death rates among men of the same age in the Finnish general population. The respective figures for lung cancer were 19 observed and 2.1 expected. No excess mortality was found for other cancers. Among the men with asbestosis, the life expectancy was shorter for smokers than for non- and ex-smokers. (30 refs)

79-1138 Excess Risk of Lymphomas, Leukemia and Myeloma in Patients with Rheumatoid Arthritis. (Eng) Isomaki, H. A. (Rheumatism Foundation Hosp., 18120 Heinola 12, Finland); Hakulinen, T.; Joutsenlahti, U. *J Chronic Dis* 31(11): 691-696; 1978.

The incidence of malignancies among 11,483 men and 34,618 women with rheumatoid arthritis was investigated. A total of 407 neoplasms was observed in men; this was significantly higher ($p < 0.01$) than the expected number (354.1). The incidence of leukemia, lymphoma, myeloma, and respiratory cancer was significantly higher ($p < 0.001$) than in the general male population. In women, the incidence of malignancies was similar to the expected incidence. The incidence of lymphoma, myeloma, and Hodgkin's disease was significantly higher than expected ($p < 0.001$), while the incidence of stomach cancer was significantly lower ($p < 0.05$). The expected number of all lymphatic system cancers in both sexes was 59.6, compared with the 130 cases observed ($p < 0.001$). (19 refs)

79-1139 Metabolic Epidemiology of Large Bowel Cancer. Fecal Bulk and Constituents of High-Risk North American and Low-Risk Finnish Population. (Eng) Reddy, B. S. (Naylor Dana Inst., Valhalla, NY, 10595); Hedges, A. R.; Laakso, K.; Wynder, E. L. *Cancer* 42(6): 2832-2838; 1978.

The dietary pattern and fecal constituents of two populations with the greatest contrast in colon cancer incidence were studied. The first group comprised 15 healthy middle-aged men from the low-risk population in Kuopio (KP), Finland, and the second 20 age-matched healthy men from a high-risk population in the New York (NY) Metropolitan area. The av daily intake of dietary fat was 96.6 and 99.6 g/day and that of protein was 94.8 and 86.7 g/day in KP and NY, respectively. However, the sources of fat were different, a greater portion coming from dairy products in KP and from meat in NY. The KP group consumed more whole-grain bread and cereals and less green vegetables and fruits than the NY men. The frequency of bowel movements was higher and the daily total stool out-put and fecal fiber excretion were greater in KP. The concentration of fecal secondary bile acids and bacterial β -glucuronidase activity was significantly lower in KP, but the total daily excretion of these constituents was the same in both groups. The daily fecal excretion of bacterial nuclear dehydrogenase activity and of a neutral sterols was higher in KP, but the concentration of these constituents was the same in the two groups. The most likely factor contributing to the low risk of colon cancer in Finland, in spite of a high dietary intake of fat, appears to be the high intake of dietary fiber. This leads to an increase in stool bulk, which dilutes promoters such as bile acids and yet to be identified carcinogens. (29 refs)

79-1140 Flexible Sigmoidoscopy: A Potential Advance in Cancer Control. (Eng) Crespi, M. (Cancer Detection Center, Istituto Regina Elena, Viale Regina Elena 291, Rome, Italy); Casale, V.; Grassi, A. *Gastrointest Endosc* 24(6): 291-292; 1978.

The potential for a higher yield of neoplastic lesions with the use of flexible fiberoptic sigmoidoscopy is pointed out. The mean level reached in 468 subjects was 63 cm, and the av time required per exam was 6 min. Of the 56 polypoid lesions found, 30 were above 25 cm, and 19 of these were neoplastic. Fifteen of 26 polypoid lesions found below 25 cm were neoplastic. Three cancers were found; one, at 40 cm, would not have been detected by rigid sigmoidoscopy. (11 refs)

79-1141 Diffuse Pleural Mesothelioma in Trieste. A Survey Based on Autopsy Cases. (Eng) Bianchi, C. (Istituto di Anatomia e Istologia Patologica, Ospedale Maggiore, Via Stuparich, 1, 34100 Trieste, Italy); Grandi, G.; Di Bonito, L. *Tumori* 64(6): 565-570; 1978.

A survey of diffuse pleural mesothelioma in Trieste, Italy, was made based on autopsies conducted between 1971 and 1977. Definite diffuse pleural mesothelioma was diagnosed in 23 men and 3 women ranging in age from 52 to 81 yr. The interval between first symptoms and death ranged from 4 mo to 5 yr. A clinical diagnosis of pleural mesothelioma was made in 15 cases; a tumor (pulmonary, thoracic, or undeter-

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mined) was diagnosed in 6, but in 5 cases no tumor had been suspected or recognized. Mesothelioma affected the left pleura in 13 cases, the right pleura in 12, and was bilateral in 1. The most frequent site of metastasis was the lungs, followed by the mediastinal lymph nodes and liver. There was coinvolvement of the pericardium in six cases. Malignancy was histologically obvious in all cases. A history of smoking habits was obtained in 23 cases and a detailed occupational history was available in 25 cases. Fourteen patients were smokers and 22 had been occupationally exposed to asbestos for 2-43 yr. The av interval between first exposure and death was 44 yr. The intensity of exposure was moderate in all cases, and asbestos bodies were found in the lungs of 20 patients. The incidence of diffuse pleural mesothelioma in Trieste is relatively high compared with that in other countries and in other parts of Italy. (12 refs)

- 79-1142 Concentration and Distribution of Heavy Metals in Nasal Mucosa of Nickel-Exposed Workers and of Controls, Studied with Atomic Absorption Spectrophotometric Analysis and with Timm's Sulphide Silver Method.** (Eng) Torjussen, W. (Sentralsykehuset, Kristiansand, 4601 Kristiansand, Norway); Haug, F. M.; Andersen, I. *Acta Otolaryngol (Stockh)* 86(5/6): 449-463; 1978.

The nickel, copper, cobalt, zinc, and iron content of biopsy specimens from the nasal mucosa of 30 nickel-exposed individuals and 6 controls was determined by atomic absorption spectrophotometry. In addition, the possibility that the sulfide staining pattern is affected by variations in these concentrations was investigated. Although the mean concentration of nickel in the nickel-exposed subjects was greater than that in controls, this difference was not statistically significant. However, the nickel concentration in the nasal mucosa of the subjects who worked in the roasting and smelting department was significantly higher ($p < 0.02$) than that in workers in other departments. No consistent differences were found in the histochemical pattern between biopsies with high and low nickel concentrations or any of the other metals. Some difference in epithelial types between specimens from the nickel-exposed group and the control group was seen, but the staining pattern was similar for corresponding epithelial types in the two groups. Two nasal carcinomas from nickel workers were unstained with the sulfide staining method. (25 refs)

- 79-1143 Association of Kaposi's Sarcoma and Prior Immunosuppressive Therapy. A 5-Year Material of Kaposi's Sarcoma in Norway.** (Eng) Klepp, O. (Det Norske Radiumhospital, Montebello, Oslo 3, Norway); Dahl, O.; Stenwig, J. T. *Cancer* 42(6): 2626-2630; 1978.

To determine the possible role of prior immunosuppressive (IS) treatment in the development of Kaposi's sarcoma (KS), a retrospective study was made of 53 histologically diagnosed

cases of KS reported to The Cancer Registry of Norway over a 5-yr period. Four cases were excluded from the material because further information contradicted the diagnosis of KS. Of the remaining 49 cases, information concerning treatment received before the development of KS was obtained for 41. Six of the 41 patients developed KS during systemic treatment with corticosteroids; 2/6 cases had also taken azathioprine. The time from the start of medication to the first sign of KS was 1, 4, 7, and 7 mo, and 7 and 8 yr, respectively. None of the patients had undergone renal transplantation. One additional patient had received radiotherapy (4,000 rads) for a malignant lymphoma prior to the development of KS. In a control group of 242 consecutive patients hospitalized because of basal cell carcinoma of the skin, none had used systemic corticosteroid or cytotoxic drugs. Case reports of the seven patients who developed KS after IS therapy are presented. Previous studies have shown that patients treated with IS drugs after renal transplantation seem to have a higher than expected risk of developing KS. This study indicates that there is also an association between prior IS therapy and development of KS in patients who have not received a renal transplant. (28 refs)

- 79-1144 Polyps of the Large Intestine in Northern Norway.** (Eng) Eide, T. J. (Dept. Pathology, Univ. Hosp., 9012 Tromsø, Norway); Stalsberg, H. *Cancer* 42(6): 2839-2848; 1978.

Autopsy results on the incidence of large intestinal polyps in northern Norway are reported. Adenomas (AD's) of the colon and rectum were present in 68/171 men and 36/109 women > 20 yr of age. The frequency of AD's increased with age in both sexes. Hyperplastic polyps were found in 55/280 cases, and there was no variation in frequency with sex or age. Before age 65, most AD's were located in the distal half of the large intestine in both sexes. After 65 yr in men and 75 yr in women, the preferred site shifted to the proximal half. The av size and grade of adenomatous atypia increased with age, but no significant difference in grade of atypia was found between the proximal and distal halves. The occurrence of AD's was not associated with any of the common chronic diseases thought to be related to a western-style diet or to malignant or benign neoplasms in other organs. A significant association was found between the occurrence of AD and high body wt. These findings support the view that AD's are important precursors for carcinomas of the large intestine. The change in subsite distribution of AD's with age corresponds to a similar, but later change in the distribution of carcinomas, and the higher incidence of carcinomas in older men is in accordance with an earlier rise in the prevalence of AD's in men than in women. (42 refs)

- 79-1145 Fecal Bile Acids in Two Japanese Populations with Different Colon Cancer Risks.** (Eng) Mow-er, H. F. (Dept. Biochemistry and Biophysics, John A. Burns

Sch. Medicine, Univ. Hawaii, Honolulu, HI, 96822); Ray, R. M.; Shoff, R.; Stemmermann, G. N.; Nomura, A.; Glober, G. A.; Kamiyama, S.; Shimada, A.; Yamakawa, H. *Cancer Res* 39(2, Part 1): 328-331; 1979.

The fecal bile acid patterns in two ethnically similar but geographically separate groups with markedly different colon cancer risk patterns were compared to examine the hypothesis that persons with higher levels of total and degraded fecal bile acids are at greater risk of colon cancer. Stool specimens were collected from 122 Japanese subjects living in Akita, Japan (JJ: the lower risk group), and from 247 Japanese subjects living in Hawaii (HJ: the higher risk group) and analyzed by gas chromatography. A diet-recall questionnaire designed to quantitate recent intakes of specific Western or Japanese food items was administered, and certain physiological data were obtained. HJ men were significantly taller and heavier and had greater hematocrit values than did JJ men who, on the other hand, had higher levels of systolic blood pressure. HJ women had slightly greater hematocrit values than did JJ women. With respect to Western foods, HJ men and women ate significantly more beef, bacon, lettuce, celery, and coffee than their counterparts in Japan, whereas JJ men and women ate significantly more dried fish, soybean curd, rice, pickled Chinese cabbage, pickled turnip, pickled plum, and genmai cha tea. More persons in Japan than in Hawaii had measureable levels of lithocholic, chenodeoxycholic, and ursodeoxycholic acids. HJ men and women had higher mean values for deoxycholic and cholic acids and for three unidentified degraded bile acids, whereas the JJ subjects had higher values for one unknown degraded bile acid. The results neither disprove nor support a major role for bile acids in the etiology of large-bowel cancer. It is possible that the higher frequency of colon cancer in the HJ population is due to an as yet unidentified carcinogen in human fecal specimens. (20 refs)

- 79-1146** Incidence of Leukemia in Atomic Bomb Survivors Belonging to a Fixed Cohort in Hiroshima and Nagasaki, 1950-71: Radiation Dose, Years after Exposure, Age at Exposure, and Type of Leukemia. (Eng) Ichimaru, M. (Dept. Hematology, Atomic Disease Inst., Nagasaki Univ. Sch. Medicine, Nagasaki, Japan); Ishimaru, T.; Belsky, J. L. *J Radiat Res (Tokyo)* 19(3): 262-282; 1978.

The leukemogenic effect of atomic radiation in atomic bomb survivors was examined in relation to age at the time of the bomb (ATB), latent period, and type of leukemia for the period 1950-1971. Confirmed cases of leukemia (136 cases) in the Leukemia Registry at the Atomic Bomb Casualty Commission, a fixed cohort of 109,000 subjects, and dose estimates based on the simple sum of gamma and neutron doses (tentative 1965 total dose) provided the basis for the analysis. The latent period was divided into three segments: 5-10, 10-15, and 15-26 yr after exposure. The larger the exposure dose and the younger the age ATB, the greater was the effect in the early period and the more rapid the decline in risk in subse-

quent years. In the oldest group, ≥ 45 ATB, the increase in risk appeared later and was sustained during 1960-1971. Chronic granulocytic leukemia contributed substantially to the total leukemogenic effect initially, but made little contribution after 1955. Age ATB played an important role in relation to latency period and type of leukemia. The onset of acute leukemia tended to be earlier in those who were young ATB than in those who were older. The effect of atomic radiation on the incidence of leukemia in atomic survivors is now greatly reduced and is continuing to decline, but the incidence in 1966-1971 was still greater than expected, especially in Hiroshima. In Nagasaki, no case of leukemia was reported among the high-dose subjects from July 1966 through 1971. (38 refs)

- 79-1147** Carcinogenic Hazard from Natural Background Radiation in Japan. (Eng) Ujeno, Y. (Dept. Experimental Radiology, Faculty Medicine, Kyoto Univ., Sakyo-ku, Kyoto 606, Japan). *J Radiat Res (Tokyo)* 19(3): 205-212; 1978.

The relationship between natural background radiation and death from cancer in 329 cities and counties in Japan was analyzed with respect to published radiation surveys and epidemiological data. The max radiation dose observed was 159.2 mR/yr and the minimum dose was 39.4 mR/yr. The incidence of male and female deaths from stomach cancer and male deaths from rectal cancer increased with increasing natural background radiation dose. Mortality from other types of cancer (esophagus, large intestine, pancreas, lung, breast, and uterus) did not show such a positive correlation. (13 refs)

- 79-1148** Relation of Radiation to Gastric Carcinoma Observed in Autopsy Cases in a Fixed Population, Hiroshima and Nagasaki, 1961-74. (Eng) Yamamoto, T. (Dept. Pathology, Radiation Effects Res. Foundation, Hiroshima 730, Japan); Shimizu, Y. *J Radiat Res (Tokyo)* 19(3): 213-227; 1978.

The relation of atomic bomb radiation to 535 cases of gastric carcinoma among 4,694 deaths occurring in a fixed population of atomic bomb survivors in Hiroshima and Nagasaki who were autopsied between 1961 and 1974 was examined. The proportion of autopsy-diagnosed gastric carcinoma cases tended to be high in the high-dose group, especially in Nagasaki, but it could not be concluded that there is a relation between gastric carcinoma and radiation in this study. There were no significant differences in the histologic type of gastric carcinoma according to radiation dose. The degree of extension of tumor cells into the gastric wall and the degree of metastasis to the lymph nodes were increased in the high-dose group. (15 refs)

- 79-1149 Gastric Cancer in Colombia. IV. Nitrite and Other Ions in Gastric Contents of Residents from a High-Risk Region.** (Eng) Tannenbaum, S. R. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139); Moran, D.; Rand, W.; Cuello, C.; Correa, P. *J Natl Cancer Inst* 62(1): 9-12; 1979.

The gastric juice of two groups of subjects from a region of high gastric cancer risk in southern Colombia was analyzed for nitrate, nitrite, thiocyanate, chloride, and pH. Group 1 comprised 55 subjects with previously undefined gastric pathology, and Group 2 comprised 18 subjects for whom gastric biopsy data were available (4 intestinal metaplasia, 7 chronic atrophic gastritis, 6 superficial gastritis, 10 necrosis of neck glands, 1 normal; some subjects had multiple pathologies). The nitrite level of many Group 1 members was several orders of magnitude higher than those reported previously; however, Group 1 samples were thawed and refrozen, and these levels may not be accurate. Although Group 2 levels were somewhat lower than those of Group 1, they were still 10 to 100 times higher than those reported previously. The patients could be broken down into two subgroups, those with gastric pH < 5 or > 5, respectively. In individuals with pH > 5 (28 Group 1 subjects, 9 Group 2 subjects) nitrate and nitrite contents were related linearly; nitrite was significantly higher in both Group 1 (90 times) and Group 2 (20 times) members of this subgroup. No correlation between pH, thiocyanate, and/or chloride and the other measured parameters was noted, and there was no variation of Zn, Ca, Cu, K, Na, Mg, or Fe ions between the high and low nitrate groups. The only Group 2 subject with a low nitrite content and pH > 5 was the only one with a normal mucosa. This is the first report of patients with gastric pathology related to a precancerous state showing high levels of a putative carcinogen precursor, and it supports the hypothesis of the intragastric bacterial reduction of nitrate to nitrite with concomitant formation of carcinogenic N-nitroso compounds. (15 refs)

- 79-1150 Gastric Secretion in Individuals from Regions with Different Stomach Cancer Morbidity.** (Rus) Il'enkova, M. K. (Dept. Epidemiology Malignant Tumors, Cancer Res. Center, Moscow, USSR). *Lab Delo* (11): 668-671; 1978.

To evaluate the possible association between anacid gastritis and cancer of the stomach, gastric juice acidity was studied in individuals from regions with a high and low incidence of stomach cancer. It was found that in regions with a high incidence of stomach cancer, most of the population had hypoacidity of the gastric juice, but in regions with a low incidence of stomach cancer, most of the individuals had normal acidity or hyperacidity of the gastric juice. (10 refs)

- 79-1151 Geographical Distribution of Malignant Tumors of the Larynx in Georgian SSR.** (Rus)

Mgaloblishvili, G. N. (Dept. Otorhinolaryngology, Cancer Res. Center, Tbilisi, USSR); Dzhordzhadze, N. A.; Gogeliani, N. K.; Gobronidze, I. A.; Ebraldidze, D. B. *Vestn Otorinolaringol* (6): 77; 1978.

An attempt was made to determine the geographical distribution of malignant tumors of the larynx in Georgian SSR (USSR) and to evaluate the role of environmental factors of laryngeal cancer morbidity. Of 136 patients, 92 had cancer of the nasopharynx, 30 had cancer of the oropharynx, and 14 had cancer of the laryngopharynx. There was a significant association between the nasopharyngeal cancers and alcohol consumption and exposure to dust, smoke, and bordeaux mixture (fungicide made by reaction of copper sulfate, lime, and water). (no refs)

- 79-1152 Non-fibrous Mineral Dusts and Malignant Tumors: An Epidemiological Study of Mortality.** (Eng) Katsnelson, B. A. (Sverdlovsk Inst. Industrial Hygiene and Occupational Diseases, Repin Str. 2, 620014 Sverdlovsk, USSR); Mokronosova, K. A. *J Occup Med* 21(1): 15-20; 1979.

Mortality due to malignant tumors associated with nonfibrous mineral dusts in the workplace was analyzed epidemiologically by relating the the number of cancer deaths registered at five companies during a 21- to 27-yr span to the number of man-years of work for all employees during the same period. The companies comprised a plant producing silica firebricks, two plants producing aluminosilicate firebricks, a gold mine, and a company for mining, grinding, and processing talc. Death rates were compared with age-rates in a control population. The observed death rate for gastric and lung cancer and tumors of all sites was significantly greater than that expected for both men and women at the talc plant, leading to the conclusion that talc dust is a carcinogen. In industries connected with silica dust, the relative risk of death from lung and gastric cancer and other malignant tumors was enhanced considerably for men but to a much lesser degree and not in all occupations for women. This indicates that silica-containing dusts only potentiate the action of some other carcinogen(s) with which men are in contact much more than women. The data on smoking habits among men and women at two of the companies suggest that the polycyclic aromatic hydrocarbons in tobacco smoke are the carcinogenic factor in these cases. The data also indicate that silicosis apparently predisposes to the development of malignant tumors. (35 refs)

- 79-1153 Relative Genealogic Incidence of Certain "Civilization Diseases" in a Geriatric Population Versus Pregeriatric Groups.** (Eng) Zdichynec, B. (Internal Disease Div., Regional Inst. Natl. Health, Hosp. and Polyclinic, 39464 Pocatky, Czechoslovakia); Stransky, P.;

Hartmann, M.; Holas, V.; Konrad, J.; Hogen, J.; Svatos, Z.; Sabl, J. *J Am Geriatr Soc* 26(12): 534-539; 1978.

The incidence of "civilization diseases" (including malignant tumors) among persons aged 70-105 yr was determined and compared with the incidence in men aged <40 with myocardial infarction and in women and men aged <60 with stroke. The incidence of malignant tumors was relatively lower in men and women aged 90-105 than in those aged 70-79 and 80-89, but the differences were not significant. Genealogic differences in the incidence of malignant tumors were not pronounced. (16 refs)

- 79-1154 Correlation Between Tuberculosis and Lung Cancer. A Regression Analysis.** (Cze) Simecek, C. (Klinika tuberkulozy a respiracnich nemoci, FVL KU, Lesni 59, 312 12 Plzen, Czechoslovakia); Simeckova, B. *Stud Pneumol Phthisiol Cech* 38(8): 518-521; 1978.

The correlation between lung cancer incidence and pulmonary tuberculosis was studied in various districts of West Bohemia in 1977. A correlation coefficient of 0.849 and a linear regression equation (cancer incidence = $30.4 + 0.637$ tuberculosis incidence) were calculated. The close correlation cannot be explained by differences in the age of the population ($r = 0.535$) or by differences in the quality of health service, because districts serviced by the same phthisiological department are interspersed among districts with high and low incidence. The findings indicate that the lesions caused by tuberculosis are a significant factor influencing lung cancer incidence. (10 refs)

- 79-1155 Neoplasms in Tasmanian Devils (*Sarcophilus harrisii*).** (Eng) Griner, L. A. (Pathology Dept., Zoological Society San Diego, P.O. Box 551, San Diego, CA, 92112). *J Natl Cancer Inst* 62(3): 589-595; 1979.

The 50% incidence of spontaneous neoplasms and preneoplastic hyperplasia in 18 necropsied Tasmanian devils at one zoo is believed to be unusually high for any mammalian species. The occurrence of multiple concomitant tumors in 6/9 animals makes the incidence even more remarkable. With the exception of one leiomyoma and one lymphosarcoma, all tumors were of epithelial origin. Six of 10 females and 3/8 males had neoplasms. The case reports of the affected animals are presented. (9 refs.)

- 79-1156 Mesothelioma after Crocidolite Exposure During Gas Mask Manufacture.** (Eng) McDonald, A. D. (Dept. Epidemiology and Health, McGill Univ., Montreal, Canada); McDonald, J. C. *Environ Res* 17(3): 340-346; 1978.

The pattern of mortality among 199 Canadians who were occupationally exposed to crocidolite between 1939 and 1942 and who were subsequently traced to the end of 1975 is described. Of a total of 56 deaths in this cohort, 23 were from malignant disease, including 9 from mesothelioma and 8 from lung cancer. Six of the nine mesothelioma cases involved the peritoneum. The duration of exposure to crocidolite among the mesothelioma cases varied from 4 mo to 3 yr, and the latency period to death was ≤ 36 yr from the first exposure. Two additional cases of mesothelioma were uncovered in another study of the employees of one of the three factories surveyed in this study. Four individuals in the present study died of pneumoconiosis. Comparison of the crocidolite-exposed workers with a cohort of chrysotile miners and millers showed that mesothelioma was 60-fold more frequent and lung cancer was twice as frequent in the crocidolite cohort, that the proportion of deaths from other malignant diseases was similar in the two cohorts, and that only 1/11 mesotheliomas in the chrysotile cohort involved the peritoneum. The continued use of crocidolite would appear difficult to justify except under the strictest possible control. (11 refs)

- 79-1157 Epidemiology of Dysplasia and Carcinoma In Situ of the Uterine Cervix.** (Spa) Valdivia Ponce, E. (Servicio de Oncologia Ginecologica, Hosp. Central No 2 del Seg. Social del Peru, Lima, Peru); Nunez Vidallon, R.; Garcia La Madrid, M.; Vigil, R. C.; Hiromoto, T.; Campos Rivera, A. *Ginecol Obstet (Lima)* 22(1): 11-21; 1976.

The incidence of dysplasia and carcinoma in situ of the uterine cervix was studied in 97,996 cytological tests during 15-yr period in Peru. Carcinoma in situ was diagnosed in 128 cases, carcinoma Stage Ia in 35, Stage Ib in 27, Stage II in 45, Stage III in 19, and Stage IV in 13. Cervical dysplasia was found in 60 cases; the dysplasia was mild in 5 cases, moderate in 36, and severe in 19. The median age of these 60 patients was 36.5 yr (33.66 in mild dysplasia, 37.83 yr in moderate dysplasia, and 36.58 yr in severe dysplasia). Fifty-five patients were married; age at the time of first intercourse was 15-24 yr in 45 cases. The median number of children per patient was 3.61. Five patients with dysplasia subsequently developed carcinoma in situ and/or microinvasive carcinoma of the cervix. The findings suggest that cervical dysplasia and carcinoma in situ can be precursors of invasive growth. (10 refs)

- 79-1158 Nine Years Screening for Cervical Cancer: Influence on Incidence and Mortality.** (Eng) Mobius, G. (Dept. Pathology, District Hosp. Schwerin, Schwerin, E. Germany); Geiling, J. *Cancer Cytol* 18(2): 13-17; 1978.

The morbidity and mortality experience of women undergoing cytologic screening for cervical cancer between 1967 and 1976 in the district of Schwerin, East Germany (population,

600,000), is reported. The number of women examined increased from 3,000 in 1967 to 47,000 in 1972 to 60,000 in 1976. The number of positive cytological findings increased sharply from 1967 to 1972, presumably due to a "catching-up" effect, and it fluctuated between 4% and 8%. This constitutes the prevalence rate. After 1972, the exams consisted of an increasing number of reexaminations, and thus the prevalence rate was replaced by the incidence rate, which leveled to 3.5%-3.2% during 1974-1976. The rapid increase in the number of carcinomas in situ from 1967 to 1972 (from 59 to 382) was followed, in spite of marked increases in the number of cytological exams, by a decrease to 163 in 1977. The total number of invasive carcinomas dropped from 137 in 1970 to 85 in 1977. In addition, the ratio of invasive carcinomas to carcinomas in situ decreased significantly over the study period. The av age at diagnosis for patients with carcinoma in situ was 39-40 yr, for those with microcarcinoma 33-52 yr, and for those with invasive carcinoma 51-58 yr. Whereas the annual number of deaths due to breast cancer (which has a similar incidence rate) fluctuated only slightly in the district from 1969 to 1976, that due to carcinoma of the cervix uteri decreased from a max of 80 in 1969 to 39 in 1976. (no refs)

- 79-1159 Diagnosis of Stomach Cancer--A Retrospective Analysis.** (Ger) Grungreiff, K. (Medizinische Akademie Magdeburg, Medizinische Klinik, Leipziger Strasse 44, DDR-301 Magdeburg, E. Germany); Hofs, R.; Kleine, F. D.; Hofs, T.; Kleine, S. *Dtsch Gesundheitsw* 33(46): 2168-2171; 1978.

Gastroscopic and x-ray findings were compared retrospectively for 323 patients, 65 of whom were found to have stomach cancer. The correct diagnosis was given by x-rays in 69.3% of the cases and by gastroscopy in 90.7%. Previous stomach resection, pernicious anemia, stomach ulcers, and polyps are considered special indications for gastroscopy. (46 refs)

- 79-1160 Epidemiological Factors Related to the Malignant Neoplasms in Ataxia-Telangiectasia Families.** (Eng) Daly, M. B. (Biological Sciences Res. Center, Univ. North Carolina, Chapel Hill, NC, 27514); Swift, M. *J Chronic Dis* 31(9/10): 625-634; 1978.

Twenty-seven ataxia-telangiectasia (AT) families were examined for selected epidemiological characteristics to see if risk factors other than the AT gene could explain the increase in deaths from cancer in general and from carcinomas of the biliary system, ovary, or stomach in particular. Demographic, social, and medical factors associated with these cancers could not explain their increased number or early age of onset. The results support a genetic basis for the increased susceptibility of AT heterozygotes to malignant neoplasms. (42 refs)

- 79-1161 Increase in Cancer of the Corpus Uteri in the San Francisco-Oakland Standard Metropolitan Statistical Area, 1960-75.** (Eng) Austin, D. F. (San Francisco Bay Area Resource Cancer Epidemiology, State California Dept. Health, 2151 Berkeley Way, Berkeley, CA, 94704); Roe, K. M. *J Natl Cancer Inst* 62(1): 13-16; 1979.

Data collected by the Resource for Cancer Epidemiology concerning the incidence of carcinoma of the corpus uteri (CCU) in women of the San Francisco-Oakland standard metropolitan statistical area were analyzed. The age-adjusted incidence rate of invasive CCU among white women increased from 26.3 to 47.5/100,000 between 1969 and 1975, an increase of 81%. This increase was limited to women > 50 yr of age and to invasive cancers of the endometrial lining, and it correlated with the increased affluence within this age group. The increase was noted throughout the five-county reporting area; in Alameda County, the av annual incidence of invasive CCU in the 50- to 74-yr age group tripled between 1960 and 1975. There were no increases in sarcomas, which occur in the myometrium. Based on the number of cases for which stage information was available (23%-52% of total), the distribution of stage of invasive CCU remained relatively stable between 1969 and 1975. Possible spurious causes of the increase, such as changing diagnostic criteria, better case finding, or better reporting, were examined and ruled out. The increased incidence in invasive CCU is attributed to postmenopausal estrogen-replacement therapy. (10 refs)

- 79-1162 Endometrial Cancer and Estrogen Use: Report of a Large Case-Control Study.** (Eng) Antunes, C. M. (Dept. Epidemiology, Johns Hopkins Univ. Sch. Hygiene and Public Health, Baltimore, MD); Stolley, P. D.; Rosenshein, N. B.; Davies, J. L.; Tonascia, J. A.; Brown, C.; Burnett, L.; Rutledge, A.; Pokempner, M.; Garcia, R. *N Engl J Med* 300(1): 9-13; 1979.

A case-control study was conducted of the relation between estrogen use and endometrial cancer (EC). The study population consisted of 451 patients diagnosed from 1973 through 1977 and 888 controls. The overall risk of EC was six-fold for estrogen users compared to nonusers; the relative risk was 2.0 for short-term users (< 1 yr) and 15 for long-term users (> 5 yr). Increased risk was associated with estrogen use for all histologic grades of the tumor. The risk of advanced-stage carcinoma was four-fold for estrogen users; however, the 95% confidence interval was 1.0 to 22, so that this issue is still unsettled. There was increased risk of EC with both diethylstilbestrol and conjugated estrogens, and the risk associated with cyclic use was as great as that for continuous use. The lag time between onset of postmenopausal bleeding and consultation with a physician did not vary significantly between users and nonusers. None of the patients who received estrogens had had them prescribed for the treatment of abnormal bleeding, an early sign of EC. This contradicts the speculation that the association between EC and estrogen use can be explained by swifter diagnosis for estrogen users

or treatment of early symptoms of the tumor with estrogen. (10 refs)

- 79-1163 Smoking and Health: The Association Between Smoking Behaviour, Total Mortality, and Cardiorespiratory Disease in West Central Scotland.** (Eng) Hawthorne, V. M. (Dept. Epidemiology, Univ. Michigan, Ann Arbor, MI, 48109); Fry, J. S. *J Epidemiol Commun Health* 32(4): 260-266; 1978.

In three separate surveys of the relationship between smoking and total mortality in west central Scotland, in which 18,786 people were screened between 1965 and 1975, the most marked association for any cause of death was for lung cancer. In men, current smokers suffered 88 deaths/5,944 at risk, with an estimated risk about 30 times higher than that of never smokers, who suffered 1 death/2,147 at risk. (18 refs)

- 79-1164 Mortality Experience of Styrene-Polystyrene Polymerization Workers. Initial Findings.** (Eng) Nicholson, W. J. (Environmental Sciences Lab., Dept. Community Medicine, Mount Sinai Sch. Medicine, New York, NY); Selikoff, I. J.; Seidman, H. *Scand J Work Environ Health* 4(Suppl. 2): 247-252; 1978.

A survey was made of the mortality experience of 560 subjects with ≥ 5 yr continuous employment as of 1 May 1960 at a styrene production and polymerization plant. At this plant, workers were exposed to several materials, including styrene, benzene, and ethylbenzene. The cohort was followed prospectively from 1 May 1960 or upon attainment of 10 yr of employment through 31 December 1975. The expected mortality rates were calculated with a modern life table analysis and data on the mortality experience of the general population of the US. There were 83 observed deaths vs 106.41 expected; this deficit may be a result of the "healthy worker effect". No patterns were noted when mortality experience was analyzed by extent of exposure; ie, when maintenance and production workers were compared with utility and service workers. One death was directly attributable to leukemia and one to lymphoma; a third death was accompanied by leukemia. A review of 361 additional death certificates of workers employed 6 mo or more at the plant revealed five additional cases of leukemia and four of lymphoma. Although these figures are suggestive of an excess risk, the small numbers and limited follow-up time do not provide definitive information on risk of death from leukemia and lymphoma at this plant. (6 refs)

- 79-1165 Mortality Experience of 50 Workers with Occupational Exposures to the Products of Coal Hydrogenation Processes.** (Eng) Palmer, A. (SRI International, Center Occupational and Environmental Safety Health, 333

Ravenswood Ave., Menlo Park, CA, 94025). *J Occup Med* 21(1): 41-44; 1979.

The mortality experience of coal hydrogenation plant workers diagnosed with skin cancer (10) or precancerous lesions (40) during 1955-1959 was determined, and information was collected on malignancies present at the time of death. Five of the workers had died from noncancerous causes, 16 had retired, 28 were still working, and 1 was lost to follow-up. No attempt was made to pursue the health history of each worker exhaustively, but this survey did reveal that one retired worker with precancerous lesions was currently ill with Parkinson's disease and cancer of the prostate, and one retired worker with cancerous skin lesions had lung cancer. Because of the small number of workers in the cohort and the few deaths that occurred, the data were not analyzed statistically, but apparently there is no increase in death due to systemic cancers as a result of heavy occupational exposure to high boiling oils containing polycyclic hydrocarbons, coal tar, and pitch. (8 refs)

- 79-1166 Genealogy of Cancer in a Family.** (Eng) Blatter, W. A. (Environmental Epidemiology Branch, NIH, NCI, 3C 18 Landow Bldg., Bethesda, MD, 20014); McGuire, D. B.; Mulvihill, J. J.; Lampkin, B. C.; Hananian, J.; Fraumeni, J. F. *JAMA* 241(3): 259-261; 1979.

The occurrence of cancer in the family of a boy with osteogenic sarcoma was traced. A younger brother of the proband developed acute lymphoblastic leukemia and another brother developed bilateral malignant neurilemoma. A family history going back to 1850 identified cancers in all four ancestral lines of the proband. The paternal grandmother lineage showed a concentration of seven family members affected by cancers of the bone, soft tissue, nervous tissue, breast, and bone marrow. The constellation of tumors in this family appears to fall into a recently described syndrome of multiple cancers affecting children and adults. The distribution of tumors in this and other families with this syndrome suggests an autosomal dominant mode of inheritance, with incomplete penetrance suggested by skipped generations. In some members of the present family, the genetic predisposition may have interacted with environmental determinants to produce particular tumors. (12 refs)

- 79-1167 Geographic Cluster Indices for Disease Mappings.** (Eng) Roegner, R. H. (Emory Univ., Atlanta, GA, 30322). *Diss Abstr Int B* 39(7): 3408B-3409B; 1979. (no refs)

- 79-1168 Risk of Lymphoma after Cardiac Transplantation (Letter to Editor).** (Eng) Penn, I. (Dept.

Surgery, Univ. Colorado Medical Center, Denver, CO, 80262). *Lancet* 2(8104/8105): 1385; 1978.

The increased risk of developing lymphomas was compared in cardiac and renal transplant recipients. Both groups developed lymphomas within remarkably short intervals following transplantation (av of 20 and 27 mo, respectively), and the tumors showed a predilection for the CNS in these patients compared with the general population. (5 refs)

- 79-1169 Breast-Cancer Incidence and Mortality Rates in Different Countries in Relation to Known Risk Factors and Dietary Practices.** (Eng) Gray, G. E. (Dept. Community and Family Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA); Pike, M. C.; Henderson, B. E. *Br J Cancer* 39(1): 1-7; 1979.

Breast cancer incidence and mortality rates in 34 countries were examined in relation to height, wt, age at menarche, and diet. Height and wt were correlated with total fat consumption and animal protein consumption; age at menarche was correlated with total fat, animal protein, meat, and egg consumption. Breast cancer mortality rates were most highly correlated with total fat and incidence rates were most highly correlated with animal protein. Although there were positive correlations between the three anthropometric variables and breast cancer rates, the effects of the dietary variables remained even after adjusting for height, wt, and menarche. Thus, while diet may indirectly affect breast cancer rates via its effect on height, wt, and age at menarche, it may have direct effects as well. (41 refs)

- 79-1170 Breast Cancer Risk Factors Among Screening Program Participants.** (Eng) Brinton, L. A. (Environmental Epidemiology Branch, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD, 20014); Wilimas, R. R.; Hoover, R. N.; Stegens, N. L.; Feinleib, M.; Fraumeni, J. F. *J Natl Cancer Inst* 62(1): 37-43; 1979.

To examine whether the usual risk indicators for breast cancer apply to individuals participating in screening programs, data were obtained by mailed questionnaires from 405 breast cancer patients identified during the first 2 yr of operation of the Breast Cancer Detection Demonstration Project and from a sample of 1,156 normal screenees. The breast cancer patients and controls did not differ significantly with regard to age or center. A higher proportion of the patients were single, separated, divorced, or widowed, whereas more of the controls were married. The risk of breast cancer was inversely related to the age at menarche. Parity, which was highly correlated with age at birth of the first child, was correlated with a decreased risk of breast cancer. Women with a surgical menopause at ages 45 to 49 yr were at a significantly increased risk relative to women with natural menopause at the same ages. Late age at menopause was correlated with a rela-

tively high risk, and the relative risk increased with cumulative years of menstruation. Family history of breast cancer was a statistically significant risk indicator, and relative risk increased with wt. Among women who had undergone natural menopause, an excess risk was present among those using birth control pills in the presence of breast cancer risk indicators. (25 refs)

- 79-1171 Plasma Oestradiol and Progesterone Levels in Women with Varying Degrees of Risk of Breast Cancer.** (Eng) Bulbrook, R. D. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Moore, J. W.; Clark, G. M.; Wang, D. Y.; Tong, D.; Hayward, J. L. *Eur J Cancer* 14(12): 1369-1375; 1978.

Plasma estradiol and progesterone levels were determined in 5,000 pre- and postmenopausal women and correlated with the risk of developing breast cancer. Increased risk of breast cancer in premenopausal women correlated with subnormal plasma progesterone values (< 3 nanograms/ml) in the luteal phase of the menstrual cycle and a subnormal excretion of urinary androgen metabolites. Plasma estradiol values did not vary with risk. In postmenopausal women, plasma estradiol and progesterone levels were not related to risk. One striking finding was that premenopausal women with a subnormal excretion of urinary etiocholanolone were predominantly those who, 5 yr later, had a luteal deficiency, which implies that the abnormality is not sporadic but may occur in most menstrual cycles in women at high risk. It also indicates that measurement of plasma progesterone and of urinary androgen metabolites may give the same prognostic information. It may be possible to check this should a sufficient number of the 5,000 volunteers eventually develop breast cancer. If a deficiency in the luteal phase secretion of progesterone proves to be an important determinant of risk, the correlation of such an abnormality might be possible. (16 refs)

- 79-1172 Urethral Tumours.** (Eng) Stewart, P. A. (Dept. Urology, General Infirmary, Great George St., Leeds 1, England); Anderson, C. K.; Williams, R. E.; Clark, P. B. *Br J Urol* 50(7): 583-585; 1978.

During the last 10 yr, 33/660 male patients undergoing follow-up for multiple superficial tumors of the bladder developed urethral tumors, an incidence of 5%. There was no evidence that the tumors had been disseminated by repeated endoscopic diathermy. Thirty-two patients had papillary carcinoma of the bladder and one had a single, solid, superficial carcinoma of the trigone. (1 ref)

- 79-1173 The Redundant Factor Method and Bladder Cancer Mortality.** (Eng) Barrett, J. C. (Dept. Medical Statistics and Epidemiology, London Sch. Hygiene

and Tropical Medicine, Keppel St., London WC1E 7HT, England). *J Epidemiol Commun Health* 32(4): 314-316; 1978.

It is sometimes advantageous to include all three factors of age, cohort of birth, and time (year of death) in a mortality analysis, although one of them may appear to be redundant. Use of cohorts is essential for diseases with long induction periods, such as cancer, in which a decline in cohort factors may reflect a progressive environmental diminution of a carcinogen. On the other hand, year of death may indicate a change in the accuracy or extent of coverage of death certification, affecting all age groups and occurring in a particular year, or the introduction of more effective treatment or a screening program. Both types of influences may be acting at once making it desirable to include all three factors. The problem of arbitrary linear trends contained in the solution, caused by the redundancy, can be circumvented by restricting the interpretation to those features that are free of linear trend; ie, by considering the points at which relatively large changes of slope occur. This method was applied to data on bladder cancer mortality in England and Wales during 1951-1970. The model was statistically acceptable. In this population time factors were all close to zero. The male cohort with the peak rate (born 1901) was one involved in the armed forces during World War I, and the nitrites from their large intake of tinned meats may have been a causative factor. It is more difficult to account for the peak in women born around 1920. (10 refs)

- 79-1174 Malignant Tumors in a Region of Endemic Nephropathy.** (Rus) Stoichev, I. I. (Inst. Oncology, Sofia, Bulgaria); Stoianov, I. S.; Petkova-Bocharova, T. K.; Chernozemski, I. N.; Nikolov, I. G. *Vopr Onkol* 24(12): 55-61; 1978.

Cancer morbidity and mortality indices were determined in a region of endemic nephropathy in Bulgaria. Between 1965 and 1974, 27 villages (7,399 men, 7,333 women) were examined. A total number of 657 cancer cases were recorded: the cumulative morbidity index (per 100,000) was 266.72 for men and 238.71 for women (compared with 159.45 and 165.66, respectively, among the population of a control, nonendemic region). The increase in cancer incidence was due primarily to the increased incidence of cancer of the urinary bladder (35.05 among men and 16.12 among women, vs 7.17 and 1.97, respectively, in controls) and renal pelvis (21.98 and 28.08, vs 0.61 and 4.04 in controls). (15 refs)

- 79-1175 Incidence of Mortality due to Malignant Skin Melanoma.** (Swe) Mattsson, B. (Radiumhemmet, Karolinska sjukhuset, S-104 01 Stockholm, Sweden). *Lakartidningen* 75(49): 4594-4595; 1978.

The incidence of malignant skin melanoma increased significantly in Swedish men and women alike during 1960-1972,

but the mortality rate increased significantly in men only. Although the incidence is somewhat higher in women than in men, the mortality has always been higher in men. (no refs)

- 79-1176 Opium and Oesophageal Cancer in Iran (Letter to Editor).** (Eng) Kmet, J. (9 Japljeva, 61000 Ljubljana, Yugoslavia). *Lancet* 2(8104/8105): 1371-1372; 1978.

Evidence is adduced to show that opium use is not a likely etiological factor in the prevalence of esophageal cancer in the Turkomen region of northern Iran. A normal or high occurrence of opium habits in other regions of Iran does not correlate positively with the incidence of esophageal cancer. Nutritional and immunogenetic components of this disease should be explored, and simple hypotheses regarding a genetic predisposition should not be overlooked. (1 ref)

- 79-1177 Epidemiology of Cancer of the Stomach, Gallbladder and Biliary Tract, Pancreas, and Small Intestine in Chile.** (Spa) Csendes, A. (Departamento de Cirugia, Facultad de Medicina Santiago Norte, Universidad de Chile, Santiago de Chile, Chile); Medina, E.; Braghetto, I. *Rev Med Chil* 105(12): 884-887; 1977.

Mortality due to digestive tract cancer was studied in Chile during 1971-1974. The mortality rate (per 100,000 inhabitants) was 6.7 in men and 3.6 in women for esophageal cancer, 2.5 in men and 7.1 in women for gallbladder and bile duct cancer, 3 in men and 3.1 in women for pancreatic cancer, and 0.1 in both sexes for cancer of the small intestine. (18 refs)

- 79-1178 Nine Cases of Hepatic Carcinoma in Young Patients Born and Living in the Village of Aldea la Espinilla, Rio Hondo, Zacapa, Guatemala. Multi-Factor Theory on the Genesis of Epidemic Hepatic Carcinoma: Genetic Factor, Alcoholism and Cirrhosis.** (Spa) Morales Sandoval, J. (Sala Medicina de Hombres, Hospital Regional de Zacapa, Zacapa, Guatemala); Paiz Calderon, N.; de Cordon, N.; Humberto Oliva, O.; Cordon Rubio, L.; Pernigotto, A.; Ruiz A., D. A.; Rivas O., B. C.; Morales Barrios, J.; Gonzalez Sehaw, R.; Rosal, J. E.; Molina N., M. *Nueve Casos de Hepatocarcinoma*: 79 pp.; 1978.

Nine young inhabitants (6 men and boys and 3 girls and women, aged 9-19 yr, median age 15.03 yr) of the village of Aldea la Espinilla, Rio Hondo, Guatemala (population: 332) died of hepatoma during the period from October 1966 to January 1978. The mortality is significantly higher than the av. The investigation of the socioeconomic and hygienic conditions suggests the involvement of the following etiological factors: genetic factor (consanguinity), alcoholism, and liver cirrhosis (partly related to alcoholism). Further studies will

be necessary to elucidate firmly the etiological factors in this epidemic of hepatoma. (9 refs)

cancers. Lymphomas occur frequently in cats and are believed to be due to viral infections. (3 refs)

79-1179 Ultrasonography in Diagnosis of Adrenal Tumors. (Fre) Anderegg, A. (Service de Radiologie, C.H.U. Vaudois, 1011 Lausanne, Switzerland). *J Radiol Electrol Med Nucl* 59(10): 539-543; 1978.

Among 2,600 individuals who were screened by abdominal ultrasonography over a 1-yr period, six adrenal tumors (2 carcinomas, 2 simple cysts, and 2 metastases of bronchial carcinoma) were detected. The ultrasonic signs of adrenal tumors are discussed. (2 refs)

79-1180 Common Neoplasms of Pet Animals. (Eng) Dutra, F. R. (No affiliation given). *West J Med* 128(5): 50; 1978.

A survey of the incidence of neoplasms in pets revealed a high incidence of female mammary cancer in dogs and cats and a low incidence of digestive tract, lung, uterine, and prostatic

See also:

*(Rev.): 79-0610, 79-0612, 79-0613, 79-0614, 79-0615, 79-0617, 79-0625, 79-0630, 79-0635, 79-0636, 79-0637, 79-0638, 79-0639, 79-0640, 79-0641, 79-0643, 79-0645, 79-0646, 79-0647, 79-0648, 79-0649.

*(Chem.): 79-0651, 79-0652, 79-0658, 79-0661, 79-0666, 79-0667, 79-0672, 79-0692, 79-0704, 79-0710, 79-0712, 79-0716, 79-0752, 79-0753, 79-0772, 79-0794, 79-0819, 79-0830, 79-0843, 79-0857, 79-0873, 79-0905, 79-0906, 79-0907.

*(Phys.): 79-0945, 79-0948.

*(Viral): 79-0966, 79-0994, 79-1014, 79-1017, 79-1020.

*(Path.): 79-1081, 79-1095, 79-1120, 79-1129.

MISCELLANEOUS

79-1181 **Aplastic Carcinoma in Diabetic Mice: Hyperglycemia-suppressed Proliferation Rate and Insulin Synthesis by Tumor Cells.** (Eng) Pavelic, K. (Dept. Experimental Biology and Medicine, "Rugjer Boskovic" Inst., P.O. Box 1016, 41001 Zagreb, Bijenicka c. 54, Croatia, Yugoslavia). *J Natl Cancer Inst* 62(1): 139-141; 1979.

The growth of a successively transplanted aplastic carcinoma was studied in diabetic and normoinsulinemic, hyperglycemic male CBA/H mice. The animals were divided into three experimental groups: mice with alloxan-induced diabetes, normal mice in which daily ip glucose administration caused severe hyperglycemia, and mice treated daily with glucose + 8 IU insulin. All mice were inoculated im with 1×10^6 tumor cells. Tumor cell suspensions from tumor bearers (first generation tumors) were injected into similarly treated mice to produce second-generation tumors. The procedure was repeated to produce subsequent tumor generations. Although the rate of tumor growth was originally suppressed in diabetic mice, it increased with each subsequent transplantation. The mean tumor wt and immunologically reactive insulin level also increased, whereas mean survival time and serum glucose level progressively decreased. In contrast, tumor growth was suppressed by hyperglycemia. The wt of the first-generation tumor in hyperglycemic mice was approx half that found in control mice with normal levels, and successive transplantation into other hyperglycemic mice did not result in enhanced tumor proliferation. The insulin level was considerably below normal in all nondiabetic animals with tumors independent of glucose administration, but when insulin was injected into hyperglycemic tumor bearers, there were no differences in mean survival time or tumor wt from normoglycemic tumor-bearing mice. The enhanced proliferation of aplastic carcinoma in diabetic mice was caused by de novo insulin synthesis, probably by the tumor cells themselves. (12 refs)

79-1182 **Low-Density Lipoprotein (LDL) Receptor Activity in Human Acute Myelogenous Leukemia Cells.** (Eng) Ho, Y. K. (Dept. Molecular Genetics, Univ. Texas Health Science Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX, 75235); Smith, R. G.; Brown, M. S.; Goldstein, J. L. *Blood* 52(6): 1099-1114; 1978.

The receptor mediated uptake of low-density lipoprotein (LDL) was measured in cells of patients with different forms of leukemia. The rate of receptor-mediated uptake and high-affinity degradation of ^{125}I -labeled LDL was 3- to 100-fold higher in blood mononuclear cells from 7 patients

with acute myelogenous leukemia (AML) than in cells from 18 healthy subjects and 21 patients with acute and chronic lymphocytic leukemias, infectious mononucleosis, and non-hematologic malignancies. The rate of cholesterol (CE) synthesis from ^{14}C -acetate was also higher (2- to 30-fold) in the AML cells. The total rate of CE input (ie, the sum of LDL-derived and endogenously synthesized CE) was, on the av, ninefold higher in the AML cells than in mononuclear cells from normal subjects. In both the normal and AML cells, >90% of the CE input was derived from receptor-mediated degradation of LDL and <10% from CE synthesized within the cell. Despite the higher input of CE in the AML cells, their content of CE, as measured by the CE:protein ratio, was 50% lower than that in normal mononuclear cells. These data indicate that the turnover of cellular CE is more rapid in AML cells than in normal mononuclear cells. This enhanced turnover might be due to a more rapid rate of utilization of CE for cellular growth or to a more rapid efflux of cellular CE. The resultant depletion of cellular CE elicits both a higher LDL receptor activity and a higher rate of CE synthesis in these leukemic cells. (31 refs)

79-1183 **Suppression by Potassium Thiocyanate of Preneoplastic Development of Mammary Glands in Female Mice.** (Eng) Nagasawa, H. (Pharmacology Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan); Yanai, R.; Nakajima, Y. *IRCS Med Sci (Cancer)* 6(11): 450; 1978.

To help elucidate thyroid function in mammary tumorigenesis, the effects of potassium thiocyanate (KSCN, 0.1% or 0.3% in the drinking water for 5 or 12 wk) on the development of hyperplastic alveolar nodules (HAN) in female SHN mice and the development of pregnancy-dependent mammary tumors (PDMT) in female GR/A mice were determined. Compared with untreated controls, the number of HAN was significantly reduced in KSCN-treated mice. HAN size did not differ between groups and there was no difference in number of HAN between the 0.1% and 0.3% KSCN groups. Body wt gain was somewhat retarded in the 0.3% KSCN group. The incidence of PDMT was also significantly reduced by KSCN treatment, and av PDMT size was larger in controls than in treated mice. The number of PDMT per mouse, the percentage of mice becoming pregnant, and litter size did not differ significantly between groups. The results indicate that KSCN-induced hypothyroidism suppresses the preneoplastic development of the mammary glands in mice

without seriously affecting normal physiological function. (3 refs)

- 79-1184** Pyrimidine (3'-5') Purine Base Sequence Preference for Intercalation into RNAs (Meeting Abstract). (Eng) Broyde, S. (Biology Dept., New York Univ., New York, NY, 10003); Hingerty, B. *Biophys J* 25(2, part 2): 221a; 1979. (1 ref)

- 79-1185** In Vitro Mutagenesis of a Circular DNA Molecule by Using Synthetic Restriction Sites. (Eng) Heffron, F. (Dept. Biochemistry and Biophysics, Univ. California, San Francisco, CA, 94143); So, M.; McCarthy, B. J. *Proc Natl Acad Sci USA* 75(12): 6012-6016; 1978.

A technique for the in vitro mutagenesis of a circular DNA molecule is described in which synthetic oligodeoxynucleotides are used as mutagens encoding a restriction endonuclease recognition site. The circular plasmid DNA is linearized by nuclease treatment, ligated to the oligomer, treated with the cognate restriction endonuclease to generate overlapping single-stranded DNA tails, and resealed. A new circular plasmid DNA into which a single new restriction site has been randomly inserted is produced. The technique allows large numbers of mutants to be isolated at defined sites that are readily localized on the physical map through restriction endonuclease mapping. Rearrangements such as duplications and deletions can be engineered at will by using the added restriction sites. This technique was used to produce a fine-structure map of the ColE1 derivative RSF1050, 60% of which is a transposable DNA sequence encoding the TEM β -lactamase (Tn3). Most mutations within Tn3 abolished transposition, but mutations mapping within a narrow region of Tn3 resulted in an increased frequency of Tn3 transposition. This technique has numerous applications, such as inserting additional amino acid sequences to alter protein structure, inserting stop codons to determine reading frame, or in DNA sequencing. (35 refs)

- 79-1186** Mechanisms of Carcinogenesis Associated with DNA Repair. (Rus) Sasukhina, G. P. (Inst. General Genetics, Moscow, USSR). *Arkhh Patol* 40(10): 79-83; 1978.

Current data on the association between malignant transformation and DNA repair activity are summarized. A deficiency of the early stages of DNA repair was detected in the cells

of patients with hereditary diseases such as xeroderma pigmentosum, Fanconi's anemia, ataxia telangiectasia, Bloom's syndrome, and Down's syndrome. These diseases are characterized by an increased frequency of malignant transformation. In vitro experiments showed that various physical and chemical carcinogens do not induce unscheduled DNA synthesis in the cells of these patients. (24 refs)

- 79-1187** Multiple Pathways of Intrareplication (Postreplication) Repair in *E. coli* K-12 (Meeting Abstract). (Eng) Rothman, R. H. (Dept. Biology, Brookhaven Natl. Lab., Upton, NY, 11973); Clark, A. J. *Biophys J* 25(2, part 2): 156a; 1979. (3 refs)

- 79-1188** Improvement in the Sensitivity of DNA Polymerase I-Deficient *Escherichia coli* for Detecting Mutagens and Carcinogens. (Eng) Venturini, S. (Inst. Microbiology, Univ. Trieste, Trieste, Italy); Monti-Bragadin, C. *Appl Environ Microbiol* 36(6): 794-797; 1978.

The sensitivity of *Escherichia coli* strains lacking DNA polymerase I activity to the antibacterial activity of mutagens and carcinogens was increased if the strain also carried a *lexA* mutation and/or the R391 plasmid. The effects of the *lexA* mutation and plasmid appeared to be additive. The differential sensitivity of this altered strain could be adapted as a preliminary screening test for mutagens and potential carcinogens. (17 refs)

- 79-1189** Adenosine Deaminase, Terminal Deoxynucleotidyl Transferase (TdT), and Cell Surface Markers in Childhood Acute Leukemia. (Eng) Coleman, M. S. (Dept. Biochemistry, Univ. Kentucky Coll. Medicine, Lexington, KY, 40506); Greenwood, M. F.; Hutton, J. J.; Holland, P.; Lampkin, B.; Krill, C.; Kastelic, J. E. *Blood* 52(6): 1125-1131; 1978.

A systematic study of 26 children with acute leukemia indicated that measurements of adenosine deaminase and terminal deoxynucleotidyl transferase distinguish biochemical subtypes of acute lymphoid leukemia and that they complement measurements of cell-surface markers. (29 refs)

- 79-1190 "Spontaneous" Neoplastic Transformation In Vitro of Epithelial Cell Strains of Rat Liver: Cytology, Growth and Enzymatic Activities.** (Eng) Morel-Chany, E. (Institut de Recherches Scientifiques sur le Cancer, B.P. No. 8, 94800 Villejuif, France); Guillouzo, C.; Trincal, G.; Szajnert, M. F. *Eur J Cancer* 14(12): 1341-1347, 1349-1352; 1978.

The principal cytological, growth, and functional changes that appeared in three isolated rat liver epithelial cell lines as they were spontaneously transformed in culture are described, and the posttransformation characteristics were compared with those of LF hepatoma cells. The three lines (FI, FII, and FIII) were isolated from the normal liver of 10-day-old Fischer or Commentary rats; the hepatoma cells were derived from a transplantable tumor. During the first passages, FI, FII, and FIII cells had a flattened epithelial shape and they adhered strongly to the substrate and to their neighbors. FI cells began to show a progressive decrease in adhesion from the 18th to the 30th passage. Gradual overlapping was observed as early as the 13th passage. The protein/-cell ratio in the FI cultures increased by a factor of 3, similar to the hepatoma cultures. The adhesiveness of the FIII cells also decreased progressively, but that of the FII cells did not change. FI cells gave rise to colonies in soft agar and induced tumors 4-9 mo after ip injection of $2-3 \times 10^6$ cells into syngeneic newborn rats; LF cells induced tumors 10 days after injection. FIII cells never produced colonies in soft agar and were not tumorigenic when injected in rats. Pyruvate kinase, aldolase, and glucose-6-phosphate dehydrogenase activity was increased in the FI cells compared to that in FII and FIII cells. The isozyme pattern was the same in all the cell lines studied. Tyrosine aminotransferase (TAT) was increased two to five times by the addition of dexamethasone to the FI cell medium. No TAT induction was observed with FII or FIII. (40 refs)

- 79-1191 Intracapillary Oxyhaemoglobin Saturation in Malignant Tumours with Central or Peripheral Blood Supply and Drainage.** (Eng) Grunewald, W. A. (Inst. Physiology, Univ. Regensburg, D-8400 Regensburg, W. Germany); Manz, R.; Mueller-Klieser, W.; Vaupel, P. *J Physiol (Lond)* 284: 57P-58P; 1978.

A cryophotometric micromethod was used to determine in vivo intracapillary oxyhemoglobin (ic HbO₂) saturation, during normoxia, in sc tissue specimens and in tissue-isolated preparations of the DS rat carcinosarcoma. The former have a peripheral, the latter a central blood supply and drainage. During the same growth stage, ic HbO₂ values were higher in the sc specimens than in the tissue-isolated preparations; ie, there is a heterogeneity of oxygenation within tumors that depends mostly on vascularization patterns. (3 refs)

- 79-1192 "Invasiveness" in Tissue Culture: A Technique for Study of Gliomas.** (Eng) Scott, R. M. (Dept. Neurosurgery, Tufts Univ. Sch. Medicine, New England Medical Center, Boston, MA); Liszczak, T. M.; Kornblith, P. L. *Surg Forum* 29: 531-533; 1978.

The application of an in vitro tissue culture technique with polycarbonate filters for assessing the invasive properties of a glioma was studied using seven human gliomas. The typical grade-1 astrocytoma grew slowly to several layers in thickness on the implanted side of the filter and did not penetrate the filter pores. All glioblastomas rapidly penetrated the filter pores and spread over both sides of the filter. Operating-room explants grew satisfactorily in some cases and could substitute for the standard coverslip cultures when stained directly and mounted flat. This technique was excellent for studying CNS material in tissue culture in that the cells could be seen as they conformed to their substrate, and mobile portions of the cell could be studied as they grew into the filter pores and on the opposite side of the filter. The technique might be used to study the effect of chemotherapeutic agents or x-irradiation on the known penetration characteristics of a particular tumor. (2 refs)

- 79-1193 Effects of Dietary Fats on Mammary Carcinoma in C3H Mice.** (Eng) Bernard, P. (Endocrinologic Pharmacology Res. Lab., Physiology Dept., Southern Illinois Univ., Carbondale, IL, 62901); Pace, M. J.; Gass, G. H. *IRCS Med Sci (Cancer)* 6(11): 489; 1978.

The effects of dietary fat on the occurrence of mammary tumors in female C3H mice with a milk tumor virus (MTV) were studied. At 4 wk of age, the animals were put on Purina Laboratory Chow diets containing 0%, 10%, 20%, or 30% added fat (Mazola oil). The study was run for 53 wk. The incidence of mammary tumors was 21% in the 0% added-fat group, 41% in the 10% added-fat group, 80% in the 20% added-fat group, and 59% in the 30% added-fat group. The increase in tumor incidence over the control value was significant for all added-fat groups. The latent period for tumor formation in all added-fat groups was reduced compared with the control group. Thus, carcinogenesis can occur as a result of a high-fat diet in the presence of MTV without the need for a chemical inducing agent. The critical level of fat needed to produce mammary carcinogenesis is approx 20%. (5 refs)

- 79-1194 Raynaud's Phenomenon. Is It a Paraneoplastic Syndrome (Letter to Editor)?** (Fre) Van der

Meulen, J. (Service de Medecine Interne, Clinique Medicale, Universite de Groningen, Groningen, France); The, T. H.; Wouda, A. A. *Nouv Presse Med* 7(43): 3935; 1978.

Two cases of Raynaud's phenomenon (digital ischemia) preceding a diagnosis of cancer are reported. The first patient, a 49-yr-old woman had Raynaud's disease for 2 yr prior to the diagnosis of a visceral adenocarcinoma. In the second patient, a 60-yr-old man, the ischemia disappeared after excision of an epidermoid tumor of the lung. (6 refs)

79-1195 Palpable Spleens: Ten-Year Follow-Up (Letter to Editor). (Eng) Ebaugh, F. G. (Stanford Univ. Medical Center, Stanford, CA, 94305); McIntyre, O. R. *Ann Intern Med* 90(1): 130-131; 1979.

A 10-yr follow-up study of 58 asymptomatic male college freshmen with palpable spleens showed that they had a significantly higher ($p < 0.05$) frequency of infection and physician office visits, compared with 178 controls. These students had normal hematocrits, reticulocyte counts, blood smears, and heterophil titers at the time the spleen was palpable. There was no evidence of lymphoreticular malignancy in the 58 subjects during the 10-yr period. (2 refs)

79-1196 Safety of Percutaneous Fine-Needle Pancreatic Biopsy: A Porcine Model. (Eng) Coel, M. N. (Radiology Service, Veterans Admin. Hosp., 3350 La Jolla Village Dr., San Diego, CA, 92161); Niwayama, G. *Invest Radiol* 13(6): 547-548; 1978.

Percutaneous fine-needle aspiration biopsy was performed in 15 normal pigs and 10 pigs with experimentally induced pancreatitis with no complications. Pancreatic cells were retrieved in 11/15 and 7/10 pigs, respectively. The results suggest that percutaneous biopsy with cytologic examination for pancreatic carcinoma can be performed in humans preoperatively and, by inference, safely. (13 refs)

79-1197 Ultrasound-Guided Fine-Needle Biopsy in Pancreatic Carcinoma. (Ger) Triller, J. (Institut für diagnostische Radiologie, Universität Bern Inselspital, CH-3010 Bern, Switzerland); Zaunbauer, W.; Fuchs, W. A.; Gretillat, P. A. *ROEFO* 129(6): 695-699; 1978.

The accuracy of fine-needle biopsy (FNB) guided by ultrasound was evaluated in 26 pancreatic carcinoma patients, and the results were correlated with radiological techniques. Needle biopsy of the pancreas proved to be an informative and economical accompanying procedure, since the sonographic demonstration of a pancreatic mass otherwise requires additional radiological and endoscopic investigations. (18 refs)

79-1198 Collagenolytic Activities of Cultured Human Malignant Melanoma Cells. (Eng) Tane, N. (Veterans Admin. Hosp., Univ. Tennessee Center Health Sciences, Memphis, TN); Hashimoto, K.; Kanzaki, T.; Ohyama, H. *J Biochem (Tokyo)* 84(5): 1171-1176; 1978.

Three independent methods (isotope release, disk electrophoresis, and segment long spacing crystallites) demonstrated that the human malignant melanoma cell can produce specific collagenase in a pure culture system. This collagenase was directly extractable from the tumor cells in active form. The high collagenase activity of the early cultures diminished with each successive subculture. (23 refs)

79-1199 A Rapid Micro Scale Method for the Detection of Lysopine and Nopaline Dehydrogenase Activities. (Eng) Otten, L. A. (Dept. Biochemistry, State Univ. Leiden, Wassenaarseweg 64, Leiden, Netherlands); Schilperoort, R. A. *Biochim Biophys Acta* 527(2): 497-500; 1978.

A rapid and sensitive paper chromatographic method, based on phenanthrene-quinone staining, was developed to determine lysopine dehydrogenase and nopaline dehydrogenase activities in crown gall tumor tissues. Enzyme activities as low as 0.2 micromole of octopine or nopaline per hour per gram of tumor tissue can be detected. As little as 5 mg of starting material is necessary. (20 refs)

79-1200 The Influence of Substrate on the Growth of a Human Colon Carcinoma Cell Line (SK-∞-1) and its Production of Carcinoembryonic Antigen (CEA) (Meeting Abstract). (Eng) Pincus, J. H. (Life Sciences Div., SRI International, Menlo Park, CA 94025); Jameson, A. K.; Fischer, M. *Fed Proc* 38(3, Part 2): 1106; 1979. (no refs)

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CARCINOGENESIS ABSTRACTS

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LANGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

ABBREVIATIONS used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μl	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μCi	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED₅₀	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO₂	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μg	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intra-dermal	SGOT	serum glutamic-oxaloacetic transaminase
IgA	immunoglobulin A	SGPT	serum glutamic-pyruvic transaminase
IgB	immunoglobulin B	soln	solution
IgG	immunoglobulin G	TCD	tissue culture dose
IgM	immunoglobulin M	TCD₅₀	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intraperitoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
Km	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD₅₀	median lethal dose		
M	molar		
μM	micromolar		

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REVIEW

- 79-1201 Chronic Diarrhea. A Practical Approach.** (Eng) Matseshe, J. W. (Mayo Clinic, Mayo Medical Sch., Rochester, MN); Phillips, S. F. *Med Clin North Am* 62(1): 141-154; 1978.

A practical approach to the diagnosis and treatment of chronic diarrhea is discussed. Chronic diarrhea is an increase in the frequency, fluidity, or volume of bowel movements relative to the usual habits for that individual lasting for > 2 wk or recurring after the initial attack. Evaluation of the patient should include the taking of an adequate history, including character of the current illness; past medical, surgical, and family history; and past history of laxative use. Primary physical examination involves a full examination of all systems and digital rectal, anoscopic, and simple stool examinations. Later tests should include examination of the stool, proctosigmoidoscopy, blood studies, barium enema, and tests for malabsorption and serum hormone levels. Among the specific causes of chronic diarrhea are functional causes, irritable colon, inflammatory bowel disease, carcinoma of the large bowel, amebic colitis, *Giardia lamblia*, metabolic disorders, and gastrointestinal hormone-producing tumors (carcinoid syndrome, Zollinger-Ellison syndrome, pancreatic cholera). Symptomatic treatment is accomplished by replacement of fluids and the administration of appropriate antidiarrheal agents. (33 refs)

- 79-1202 Chemical Carcinogens (3 Letters to Editor).** (Eng) Hooper, N. K. (Dept. Biochemistry, Univ. California, Berkeley, CA, 94720); Harris, R. H.; Ames, B. N.; Schneiderman, M. A. *Science* 203(4381): 602-603; 1979.

Two studies cited in a recent report on chemical carcinogens that support the threshold theory, one concerning vinyl chloride and one concerning chloroform, are criticized. The basic arguments that detoxifying mechanisms are overwhelmed at high dose levels and that high doses of chemicals cause pathological damage to tissues and increase their susceptibility to cancer are countered by other studies showing the opposite results. In addition, a biological model implied in the report--that logarithm of the percent of animals developing a tumor is linearly related to the logarithm of the dose--is inappropriate. (16 refs)

- 79-1203 Chapter 11. Quantitative Risk Assessment.** (Eng) Scientific Committee (Food Safety Council, 221 Teachers Bldg., Columbia, MD, 21044). *Food Cosmet Toxicol* 16(Suppl 2): 109-136; 1978.

Problems involved in quantitatively assessing the risk to humans of food substances implicated in laboratory toxicity,

mutagenicity, and/or carcinogenicity tests are reviewed. The probit, logit, one-hit, gamma multi-hit, Armitage-Doll multi-stage, and the statistico-pharmacokinetic models are discussed, and recommendations are made for a low-dose risk assessment. (38 refs)

- 79-1204 Statistical Design of Toxicity Assays: Role of Genetic Structure of Test Animal Population.** (Eng) Haseman, J. K. (Biometry Branch, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709); Hoel, D. G. *J Toxicol Environ Health* 5(1): 89-101; 1979.

The statistical aspects of strain-to-strain differences in cancer susceptibility are considered, and one strain vs multistrain testing is discussed. Previous data were examined to evaluate the magnitude of within-study, interstrain differences in tumor induction. Although there was a very high overall association between mouse strains [(C57BL/6 x C3H/Anf)_{F₁} and (C57BL/6 x AKR)_{F₁}] with respect to hepatoma induction, evidence of strain-to-strain variability was found for several compounds; ie, sodium diethyldithiocarbamate, PCNB (quintozene), bis(2-chloroethyl)ether, and potassium bis(2-hydroxyethyl)dithiocarbamate. A survey of several long-term carcinogenicity studies with DDT revealed interstrain differences in cancer susceptibility for this compound also. When data from these DDT studies were used to estimate the risk of cancer in humans, the risk estimates varied widely. Even for studies in which some increased risk was indicated, there was as much as a 1,000-fold difference in the actual risk estimates for lung tumors. Statistical calculations indicate that if susceptible subgroups do exist and if certain simplifying assumptions are made, then in many cases tumor increases can be detected more readily by studying several inbred mouse strains rather than a single outbred stock. (17 refs)

- 79-1205 Short-Term Mutagenicity Tests for Carcinogens--Their Place in Toxicological Evaluation.** (Eng) Bridges, B. (MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton BN1 9QG, England). *Invest Cell Pathol* 1(4): 293-295; 1978.

The role of short-term mutagenicity tests for carcinogens in toxicological evaluations for regulatory and decision-making purposes is considered. It has been argued that only the currently established microsome/*Salmonella typhimurium* (Ames) protocol has been validated and that departures from it should be discouraged. However, there is evidence that the liver microsome mix does not always represent the actual balance of activation and detoxification in vivo. It is suggested that the Ames test be supplemented by investigations of

the response of other cellular indicator systems and by studies of the actual balance of metabolism in the whole animals and in a range of different tissues. Such studies could then form a satisfactory basis for regulatory action and company decision-making on substances to which the public may be exposed to a significant extent. The bacteria/microsome test taken on its own does not achieve this goal. (7 refs)

- 79-1206 Chapter 6. Genetic Toxicology.** (Eng) Scientific Committee (Food Safety Council, 221 Teachers Bldg., Columbia, MD, 21044). *Food Cosmet Toxicol* 16(Suppl 2): 35-63; 1978.

The state-of-the-art in the field of mutagenicity testing is reviewed extensively. A detailed discussion of assays for determining mutagenic activity in vitro and in vivo covers the test organisms and the types of mutations investigated. (132 refs)

- 79-1207 Genetic Constitution and Response to Toxic Chemicals--An Overview.** (Eng) Womack, J. E. (Inst. Comparative Medicine, Texas A&M Univ., College Station, TX, 77843). *J Toxicol Environ Health* 5(1): 49-51; 1979.

Information that supports the argument against the use of random-bred or outbred rodents in carcinogenesis and toxicological testing is reviewed. There is no scientific justification for this practice. The frequent desire for heterozygosity in a test population can best be met by using F₁ hybrids of inbred progenitor strains. (5 refs)

- 79-1208 Genetic Aspects of Metabolic Processing of Chemical Substances.** (Eng) Thorgeirsson, S. S. (Biochemical Pharmacology Section, Lab. Chemical Pharmacology, NCI, NIH, Bethesda, MD, 20014); Wirth, P. J. *J Toxicol Environ Health* 5(1): 83-87; 1979.

Studies of the *Ah* locus in the mouse, which controls the induction of cytochrome P₁-450 and at least 10 associated monooxygenase activities, are reviewed. A single gene difference has been shown to exist between the inbred mouse strains C57BL/6N and DBA/2N in the induction of aryl hydrocarbon hydroxylase, a hepatic monooxygenase activity, and cytochrome P₁-450 (P-448) by 3-methylcholanthrene (3-MC). Studies using > 30 inbred mouse strains indicate that two-thirds are genetically responsive and about one-third are nonresponsive. Numerous other monooxygenase activities are induced by 3-MC; this induction is closely associated with the *Ah-b* allele. Differences at the *Ah* locus have been related to differences in survival time in mice given massive doses of benzo(a)pyrene, 7,12-dimethylbenz(a)anthracene, hexachlorocyclohexane (lindane), or polychlorinated biphenyls. In these cases, the survival time of the responsive strains was significantly shorter than that of the nonresponsive inbred strains. The *Ah-b* allele is also highly correlated with

acetaminophene (AAP)-induced glutathione depletion, hepatotoxicity, and increases in covalently bound AAP metabolites. Large doses of 2-acetylaminofluorene, unlike AAP, do not cause hepatic glutathione depletion, even though similar large increases were observed in the rate of N-hydroxylation of both drugs after induction of cytochrome P₁-450 by 3-MC. (16 refs)

- 79-1209 Genetic Toxicology of Bleomycin.** (Eng) Vig, B. K. (Nevada Mental Health Inst., P.O. Box 2460, Reno, NV, 89505); Lewis, R. *Mutat Res* 55(2): 121-145; 1978.

Data on the genetic toxicology of bleomycin, a class of approx 200 antibiotic compounds that differ from each other in the amine moiety, are reviewed. At low concentrations, the drugs can cause elimination of bases, particularly thymine. This results in DNA strand breakage and inhibition of cell growth, although the two effects may not be related. In general, mitotically dividing cells, especially those in G₂, are most sensitive to DNA damage, indicating that cell death may not be related to a direct effect of the antibiotic on DNA replication. The drugs cause chromosomal damage in all subphases of interphase, and they can also affect early prophase chromosomes. Bleomycin-induced breakage and cell death may be similar to those induced by densely ionizing radiations. Whereas the antibiotics affect the frequency of somatic crossing-over and produce micronuclei, the data on mutation induction and production of sister chromatic exchanges do not permit classification of the bleomycins as potent inducers of these phenomena. The genetic effects of the bleomycins can be quantitatively modified by thiol compounds, caffeine, hyperthermia, and H₂O₂. The available data do not permit assessment of genetic damage in the offspring of bleomycin-treated patients. Studies of these effects are needed, as are studies to determine the effects of bleomycins on meiosis. (130 refs)

- 79-1210 Chemical Modifications of DNA Conformation.** (Fre) Daune, M. (Laboratoire de Biophysique, Institut de Biologie Moléculaire et Cellulaire, CNRS, 15 rue Rene Descartes, 67000 Strasbourg, France). *Biochimie* 60(10): 1097-1110; 1978.

The mechanisms by which three classes of chemical carcinogens (alkylating agents, aromatic hydrocarbons, and aromatic amines) alter DNA are reviewed. It is assumed that chemical carcinogenesis occurs when a chemical agent causes a change in DNA that is perpetuated and translated into genetic deprogramming and tissue alteration. The first step in chemical carcinogenesis is fixation of a metabolite of the chemical to the DNA molecule. The structural alteration that follows can then disturb replication, transcription, or DNA repair. The methods by which biological systems repair DNA lesions induced by chemical carcinogens are described. The limitations of present knowledge of the mechanisms of chemical carcinogenesis and DNA repair are considered. (62 refs)

- 79-1211 **Studies of the Relationships Between Mutagenesis and Carcinogenesis.** (Fre) Hofnung, M. J. (Unite de Toxicologie genetique, Institut Pasteur, Paris, France). *Biochimie* 60(10): 1151-1171; 1978.

Studies of the relationship between mutagenesis and carcinogenesis are reviewed. A linear relationship was found between the dose inducing tumors in experimental animals and that inducing revertants in *Salmonella typhimurium* for aflatoxin B₁, sterigmatocystin, benzo(a)pyrene, propane sulfone, dibenz(a,h)anthracene, 4-aminobiphenyl, benzidine, and 2-naphthylamine. However, there is no direct proof of a relationship between mutagenesis and carcinogenesis. (16 refs)

- 79-1212 **Mutagens and Carcinogens.** (Eng) Brookes, P. (Chemical Carcinogenesis Div., Inst. Cancer Res., Pollards Wood Res. Station, Chalfont St. Giles, Bucks, England). *Invest Cell Pathol* 1(4): 291-293; 1978.

The relationship between mutagens and carcinogens is briefly considered. The use of radioactively labeled carcinogens led to the finding that they were bound to the DNA of treated cells. Although much of the administered carcinogen was eliminated following metabolism, a small percentage was converted to a chemically reactive form that could penetrate the nucleus and interact with DNA. The mutation theory of cancer would, therefore, predict that all ultimate carcinogens should be mutagenic, which has proved true. Several observations are consistent with the view that cancer results from a mutational event. These include epidemiological studies of childhood tumors and cell hybridization studies with normal and tumor cells. Many tumors in animals and humans are clonal. The discovery that cells from the skin of patients with xeroderma pigmentosum and ataxia telangiectasia are defective in the repair of DNA damage induced by radiation or chemicals, is strongly indicative of the role of DNA modification in cancer causation. (15 refs)

- 79-1213 **Evidence in the Experimental Animal of the Mutagenic Properties of Chemical Agents.** (Fre) Siou, G. (Laboratoire d'Histopathologie, C.E.R.T.I., 88, avenue de Paris, 78000 Versailles, France); Conan, L. *Ann Falsif Expt Chim* 71(770): 411-426; 1978.

Methods of detecting the mutagenic potential of chemical agents in laboratory mammals are reviewed. Chemicals that have proved mutagenic effects on blood and germ cells are tabulated. Results of in vivo and in vitro mutagenicity tests of six chemicals (benzomyl, methylbenzimidazole carbamate, phosphamidon, polyvinyl chloride, diquat, and captane) are compared. (55 refs)

- 79-1214 **Cocarcinogenic or Conditional Cancer-promoting Factors: New Aspects of the Etiology of Human Tumors and Molecular Mechanisms of Tumor Development.** (Ger) Hecker, E. (Institut für Biochemie, Deutsches

Krebsforschungszentrum, D-6900 Heidelberg, W. Germany). *Naturwissenschaften* 65(12): 640-648; 1978.

Findings during the last 10 yr on the sources of exogenous cocarcinogens and their mode of action are reviewed. In the mouse epidermis model, a single dose of carcinogen produces no tumors; if several doses of cocarcinogen follow, many benign tumors result. Some of these tumors progress to malignancy, possibly under the influence of a postulated progressor substance. This sequence is the basis of the "three-step" model of cancer development. Within the last 10 yr, numerous exogenous cocarcinogens were identified chemically and biologically and characterized as tumor initiators or promoters. They are the highly irritant diterpene (DTP) esters (ie, tiglliane, daphnane, and ingenane) from Euphorbiaceae and Thymelaeaceae plants. Many of these plants have long been used as teas, folk medicines, cleaning agents, or insect repellants. The high incidence of esophageal cancer among natives of Caracao has been traced to their extensive use of the Euphorbiaceae *Croton flavens*. Chemical studies have shown that the variation in the cocarcinogenicity of DTP's depends on the presence of side chains. Some DTP's (cryptic cocarcinogens) are inactive unless substituents are removed; after enzymatic action, they become cocarcinogenic. Not all DTP's that are skin irritants are cocarcinogens. Cocarcinogens increase DNA synthesis. The promoting effect of different DTP's correlates positively with the in vitro release of prostaglandin E₂ from mouse skin. These cocarcinogens also can induce virus synthesis in cells containing persistent genomes by simian virus 40 or Epstein-Barr virus. (45 refs)

- 79-1215 **Report of the Workshop on Carcinogenicity.** (Eng) Butler, W. H. (Safety Medicines Dept., Pathology Section, Imperial Chemical Industries, Ltd., Alderley Park, Macclesfield, Cheshire, England). *J Toxicol Environ Health* 5(1): 161-162; 1979.

Information presented at a workshop on the choice of animals for carcinogenicity testing is summarized briefly. Topics covered include the use of inbred vs outbred animals, the comparative influence of genetic and environmental determinants in modifying the behavior of the animal, selecting a species or strain for a specific purpose, and current regulations for carcinogenicity testing. (no refs)

- 79-1216 **Alpha-Fetoprotein as an Indicator of Early Events in Chemical Carcinogenesis.** (Eng) Sell, S. (Dept. Pathology, M-012, Univ. California at San Diego, La Jolla, CA, 92093). *ACS Symp Ser* 80: 326-341; 1978.

Properties of α -fetoprotein (AFP), its synthesis and levels during normal development, and its significance in hepatotoxic liver injury and in tumor growth and development are reviewed. It has been hypothesized that AFP acts as a signal for the organization of liver tissue into normal lobules during normal growth or regeneration. According to this hypothesis, AFP production during exposure to hepatocarcinogens

represents an inappropriate signal. Carcinogens induce a small number of immature hepatocytes (possibly stem cells) to proliferate. Under inappropriate signals for organization, some of these stem cells, perhaps only one or two per liver, eventually produce hepatocellular carcinomas. The previously accepted sequential evolution of hepatocellular carcinomas from foci of altered hepatocytes through neoplastic nodules to malignant tumors is not supported by the results of ongoing experiments. Neoplastic nodules may represent a noncancerous response of differentiated hepatocytes to carcinogen exposure. (75 refs)

- 79-1217 A Review of the Specifications and Toxicity of Synthetic Food Colors Permitted in Canada.** (Eng) Khera, K. S. (Natl. Health and Welfare Canada, Ottawa, Ontario, Canada); Munro, I. C. *CRC Crit Rev Toxicol* 6(2): 81-133; 1979.

The chemical and biological characteristics of food dyes that relate to their safety evaluation are reviewed in detail, with emphasis on those dyes whose use is permitted in Canada. These dyes include amaranth, Ponceau SX, Sunset Yellow FCF, and Citrus Red No. 2 from the azo category; tartrazine from the azopyrazolone dyes; Brilliant Blue FCF and Fast Green FCF from the triphenylmethanes; erythrosin from the xanthenes; and indigotin from the indigoid class. (608 refs)

- 79-1218 Carcinogens in Food and the Delaney Clause.** (Eng) Jukes, T. H. (Div. Medical Physics, Univ. California, Berkeley, CA, 94720). *JAMA* 241(6): 617-619; 1979.

The Delaney Clause, a statement in the Food Additives Amendment of the Federal Food, Drug, and Cosmetic Act that became a law in 1958, prohibits the addition of any substance to food that causes cancer in humans or animals. The clause does not recognize and exempt a no-effect level of a carcinogen. Many carcinogens in food, however, are from natural sources. In addition to aflatoxin, other substances in molds, such as patulin (found in 37% of apple juice samples examined by the FDA), are carcinogenic. Nitrite, which some experiments suggest is carcinogenic, is added to meat products. However, <20% of the nitrite intake is from that added to meat and >80% is in saliva, where it is produced by the action of oral bacteria on nitrates that occur in vegetables. Nitrites also react with secondary amines to produce nitrosamines, which are carcinogenic in various animals. Secondary amines of natural origin, eg, proline, occur widely in foods. Pyrolysis produces benzo(a)pyrene in many foods, including roasted coffee and smoked meats. Man-made substances such as pesticides or diethylstilbestrol (DES) may also enter the food supply. Viewed against the background of endogenous estrogen production, the effect of the max probable intake of DES from beef is inconsequential. It is concluded that the existence of the Delaney Clause has focused attention on certain food additives, but nonadditive carcinogenic substances in food may be ignored. Regulatory distinctions should not

be drawn between various carcinogens on the basis of whether they are natural or man-made. (20 refs)

- 79-1219 The Detection and Control of Mutagenic and Carcinogenic Compounds in the Environment.** (Eng) Ramel, C. (Environmental Toxicology Unit, Wallenberg Lab., Univ. Stockholm, S-104 05 Stockholm, Sweden). *Ambio* 7(5/6): 244-249; 1978.

A sequential, tiered system of mutagenicity screening is proposed as the only feasible means of identifying genotoxic substances in the environment. The suggested system comprises three levels (detection, verification, and quantification) and it should lead to a useful risk-benefit analysis of the compound under investigation. (55 refs)

- 79-1220 The Role of Insects and Other Plant Pests in Aflatoxin Contamination of Corn, Cotton, and Peanuts--A Review.** (Eng) Widstrom, N. W. (US Dept. Agriculture-SEA, Tifton, GA). *J Environ Qual* 8(1): 5-11; 1979.

The involvement of insects in the fungal infection of agricultural products and the subsequent development and production of aflatoxins is reviewed. The principal role of insects in toxin contamination is one of predisposing plant tissue to fungus invasion. There is no conclusive evidence linking the pests of peanuts with aflatoxin contamination of that crop. (62 refs)

- 79-1221 Status of the Aflatoxin Problem in Corn.** (Eng) Zuber, M. S. (Univ. Missouri-Columbia, Columbia, MO); Lillehoj, E. B. *J Environ Qual* 8(1): 1-5; 1979.

Information concerning aflatoxin contamination of corn, effects of the environment on aflatoxin levels, and methods of controlling this contamination are reviewed. Conditions in the southern US are more conducive to fungal infection and subsequent toxin production. Insects and stress conditions, such as drought, enhance the problem. A break in the pericarp is necessary for fungal invasion. The use of insect-resistant hybrids and practices that reduce stress or shift the ear development stage to miss a likely stress period are recommended. (24 refs)

- 79-1222 Bran and Experimental Colon Cancer (4 Letters to Editor).** (Eng) Newcombe, R. G. (Dept. Medical Statistics, Welsh Natl. Sch. Medicine, Heath Park, Cardiff CF4 4XN, Wales). *Lancet* 1(8107): 108; 1979.

Two previous studies, one showing a protective effect of dietary fiber against 1,2-dimethylhydrazine (DMH)-induced rat colonic cancer and the other showing no effect, are discussed. Although the former study has been justifiably criticized, the latter cannot be taken as strong evidence against a protective

effect in humans. The relevance to human carcinogenesis of the DMH animal model is questionable. A model using a strain bred for very high natural cancer risk would be more realistic. (9 refs)

- 79-1223 Polybrominated Biphenyls.** (Eng) IARC Working Group (Lyon, France). In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Polychlorinated Biphenyls and Polybrominated Biphenyls*. International Agency for Research on Cancer. (Lyon, France): 18: 107-124; 1978.

The chemical and physical data; production, use, occurrence, and analysis; and biological data relevant to the evaluation of carcinogenic risk to humans are presented for the polybrominated biphenyls (PBB's) hexabromobiphenyl (HBB), octabromobiphenyl, and decabromobiphenyl. The experimental carcinogenicity data consist of only one experiment with a commercial preparation of HBB, Firemaster FF-1. It was tested in rats by po administration of single doses. Although neoplastic changes of the liver were reported, the study was considered inadequate. Firemaster FF-1 is embryotoxic and teratogenic. Cytogenetic tests in mice were negative. No case reports or epidemiological studies of humans were available for any of the PBB's. The extensive production of PBB's, their persistence in the environment and in the body, and their use, mainly as flame retardants, indicate that widespread human exposure occurs. No evaluation of the carcinogenicity of PBB's could be made on the basis of available data. (57 refs)

- 79-1224 Polychlorinated Biphenyls.** (Eng) IARC Working Group (Lyon, France). In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Polychlorinated Biphenyls and Polybrominated Biphenyls*. International Agency for Research on Cancer. (Lyon, France): 18: 43-103; 1978.

A critical review of carcinogenicity data for 39 polychlorinated biphenyls (PCB's) is presented in terms of human risk. Experimental data showed that Kanechlor 500 and Aroclor 1254 are carcinogenic in mice and that Aroclor 1260 is carcinogenic in rats; all induced benign and malignant liver cell tumors. Kanechlor 300, 400, and 500 induced liver lesions described as multiple hyperplastic nodules. Human exposure to small amounts of PCB's is widespread as a result of environmental contamination and the high stability of these compounds. Epidemiological data provide suggestive evidence of a relationship between exposure to PCB's and the development of malignant melanoma. Further data are needed to confirm these relationships, but in the meantime, PCB's should be regarded as if they were carcinogenic to humans. Almost without exception, PCB's contain various levels of polychlorinated dibenzofurans (PCD's) as contaminants. It is not known if and to what extent PCD's play a role in the observed carcinogenic effects of PCB's. (236 refs)

- 79-1225 Polychlorinated Dibenzodioxins and Dibenzofurans--Compounds of Current Interest.**

(Swe) Rappe, C. (Dept. Organic Chemistry, Umea Univ., S-901 87 Umea, Sweden). *Lakartidningen* 16(1/2): 21-24; 1979.

Recent studies of the toxicology of dioxins and dibenzofurans are reviewed. 2,3,7,8-Tetrachlorodioxin was found to be a potent carcinogen in experimental animals, even in small doses. 1,2,3,6,7,8-hexachlorodibenzodioxin and 1,2,3,7,8,9-hexachlorodibenzodioxin also induced tumors in experimental animals. No pronounced organ specificity was found for these compounds. Polychlorinated dibenzodioxins and dibenzofurans occur as impurities in technical products such as 2,4,5-trichlorophenol and chlorinated phenols in general, and they are formed in pyrolytic reactions as well. Exposure to these carcinogens is highest in the production of (2,4,5-trichlorophenoxy)acetic acid and other chlorophenols. An epidemiological case-control study revealed an increased incidence of malignant mesenchymal soft-tissue tumors in persons exposed to phenoxy acids and chlorophenols. The tumors may be due to these substances and/or the impurities they contain. (45 refs)

- 79-1226 Concentrations of Polycyclic Aromatic Hydrocarbons in the Workplace.** (Ger) Otto, J. (Arbeitshygieneinspektion des Rates des Bezirkes Erfurt, Predigerstrasse 6, DDR-50 Erfurt, E. Germany); Schmidt, E. *Z Gesamte Hyg* 24(12): 896-898; 1978.

Polycyclic aromatic hydrocarbon levels in work areas in which carbon black is processed in the rubber industry, tar is processed, and combustion engines are used in enclosed spaces were determined by gas chromatography in the temperature range of 298-495 C. The highest levels were found in tar-processing areas (up to 29 $\mu\text{g}/\text{m}^3$). In areas involving carbon black and exhaust gas exposure, they were as high as 2.4 and 8 $\mu\text{g}/\text{m}^3$, respectively, with benzo(a)fluorene, benzo(a)anthracene, and benzo(a)pyrene predominating. (19 refs)

- 79-1227 Epithelial Cancer, Differentiation, and Vitamin A.** (Eng) Hogan, B. (Imperial Cancer Res. Fund Labs., Mill Hill, London, England). *Nature* 277(5694): 261-262; 1979.

The effects of retinoids, a class of compounds based on vitamin A, on epithelial cells in organ culture, on epithelial carcinogenesis in vivo, and on cultures of transformed and untransformed cells are reviewed. Several reports show that feeding animals high doses of retinoids, especially retinoic acid, after carcinogen treatment reduces the severity and incidence of lesions in a variety of epithelial sites (bladder, lung, and trachea). Retinoids seem to act like antipromoters, although in certain systems they have been found to act like promoters. (15 refs)

- 79-1228 Diethylstilbestrol and the Risk of Cancer (2 Letters to Editor).** (Eng) Clark, L. C. (Univ. North Carolina, Chapel Hill, NC, 27514); Portier, K. M.; Bibbo, M.; Haenszel, W. M.; Wied, G. L.; Hubby, M.; Herbst, A. L. *N Engl J Med* 300(5): 263-264; 1979.

The results of two studies in which it was concluded that diethylstilbestrol (DES) therapy does not increase cancer risk are reevaluated. A chi-square analysis of the cancer mortality data from one study indicates that DES exposure is associated with more than a twofold increase in risk for all cancers; the risk increases to 2.73 for endocrine-related tumors and to 2.89 for breast cancer. Both studies lack the statistical power to justify the conclusion that DES does not increase cancer risk. Presentation of the data with both the point estimate of risk and its associated confidence interval would aid in proper interpretation of the study results. The difference in the magnitude of relative risk between the incidence and mortality cases may be due to differences in risk between premenopausal and postmenopausal breast cancer or to the fact that mean latency is better represented by the mortality cases than by the incidence cases. In a reply, the authors of one study state that point estimates and their confidence limits were considered in reaching conclusions. The statement that mean latency is better represented by mortality cases has little foundation in any carcinogenesis models. The critics disregard the excess risk for breast cancer in the entire study group and the absence of a gradient risk for the DES-exposed women starting therapy by the 11th week, compared with those who started later. Another troublesome point is that excess risk in the premenopausal ages has not been reproduced among the postmenopausal women. These results led to the suggestion, in the original article, that the selection of mothers entering the randomized clinical trial might be a confounding factor. (3 refs)

- 79-1229 Pathology of Prenatal Diethylstilbestrol Exposure.** (Eng) Welch, W. R. (No affiliation given); Prat, J.; Robboy, S. J.; Herbst, A. L. *Pathol Annu* 13(1): 201-216; 1978.

Studies of the association between prenatal diethylstilbestrol (DES) exposure and clear cell adenocarcinoma (CCA) of the vagina or cervix are reviewed. Of > 350 cases reported to the Registry for Research on Hormonal Transplacental Carcinogenesis as of June 1977, prenatal exposure to DES or to the related nonsteroidal estrogens dienestrol or hexestrol was documented in 60%. The youngest patient was 7 yr old at the time of diagnosis and the oldest 28. Microscopically, the CCA associated with DES exposure is identical to CCA of the ovary or endometrium observed in older women. The microscopic differential diagnosis of CCA includes hyperplasia of vestigial mesonephric ducts, Arias-Stella reaction, microglandular hyperplasia, and endodermal sinus tumor. Fifty-six patients with follow-up have developed recurrences or have died. In contrast to squamous cell carcinoma of the vagina or cervix, CCA more often metastasizes to the lung or supraclavicular lymph nodes. Almost every patient in whom the tumor was detected at an asymptomatic stage is

alive and free of disease after initial therapy. The benign abnormalities that occur in 20%-95% of exposed women consist of structural malformations of the vagina and/or cervix and glandular epithelium in the vagina (adenosis) or cervix (ectropion). It is not known whether adenosis is the precursor of the CCA. However, since it has been found in > 90% of the vaginal tumors, it appears to provide the background from which the neoplasm arises. Nonmalignant abnormalities have been reported in men exposed to DES in utero. (33 refs)

- 79-1230 Toxic Agents Resulting From the Oxidative Metabolism of Steroid Hormones and Drugs.** (Eng) Horning, E. C. (Inst. Lipid Res., Baylor Coll. Medicine, Houston, TX, 77030); Thenot, J. P.; Helton, E. D. *J Toxicol Environ Health* 4(2/3): 341-361; 1978.

Mechanisms by which toxic agents result from the oxidative metabolism of steroid hormones and drugs are reviewed. The emphasis is on the structure, mode of formation, and reaction of reactive metabolites of compounds that are related to estrogenic hormones and that are known carcinogens or are associated with cancer in animal models or in humans. The types of structures and reactions included are those arising from (1) the epoxide/dihydrodiol pathway, with an epoxide as the reactive metabolite and with a postulated ionic reaction mechanism for reaction with cell components; (2) the catechol/o-quinone pathway, with an o-quinone as the reactive metabolite and with either an ionic or a neutral semiquinone radical reaction mechanism; and (3) alkylation reactions, in which a radical may be the intermediate species. The possible formation of electrophiles from diethylstilbestrol, natural estrogens, and ethinyl estradiol is discussed in terms of protein binding. Protein binding is presumptive evidence of electrophil formation, but it does not necessarily indicate that the parent compound is highly cytotoxic, mutagenic, or carcinogenic. Mutagenic and carcinogenic activity is presumed to require reaction of an electrophile with nuclear material. There is evidence for protein binding of the above estrogens as a consequence of oxidative metabolism. (71 refs)

- 79-1231 Toxins and Carcinogens in the Environment: An Observation in the Tropics.** (Eng) Bababunmi, E. A. (Dept. Biochemistry, Sch. Medicine, Univ. Ibadan, Ibadan, Nigeria). *J Toxicol Environ Health* 4(5/6): 691-699; 1978.

Reports on the presence of toxic chemicals in the foods and environment of tropical African countries, particularly Nigeria, are reviewed. The incidence of primary liver cancer in these countries is the highest in the world, possibly due to a multiple chemical factor etiology. Toxins identified so far include hypoglycin, dioscorine, sapotoxin, cycasin (a cycad diet has induced malignant tumors of the liver in a number of species), mushroom toxin, capsaicin (red pepper toxin), halogeton toxin (oxalic acid), cyanogen (prussic acid), fluorooleic acid, and some N-nitroso compounds, such as dime-

thyl nitrosamine and diethylnitrosamine, which have been detected in several alcoholic beverages. The fungal contaminants aflatoxin and palmotoxin have been identified on a variety of foodstuffs. Some plants from which herbal teas are brewed contain carcinogens, some of which are pyrrolizidine alkaloids. The emergence of some African countries from the underdeveloped to the developing state has resulted in the introduction of foreign toxic chemicals in such forms as medicine, pesticides, and food additives; ie, quinine, DDT, and cyclamates. (27 refs)

- 79-1232 Carcinogenic Substances in Water.** (Cze) Bartacek, J. (Katedra technologie vody a prostredi, VSCHT, Prague, Czechoslovakia). *Vys SK Chem Technol Praze* 22: 5-49; 1978.

Studies of the occurrence, elimination, and determination of carcinogens in various types of water are reviewed, with special regard to polycyclic aromatic hydrocarbons (PAH). The major PAH's found in water include benzo(a)pyrene, benzo(e)pyrene, anthracene, benz(a)anthracene, 9,10-dimethylbenz(a)anthracene, dibenz(a,h)anthracene, phenanthrene, chrysene, pyrene, fluoranthene, perylene, and 3-methylcholanthrene. Benzo(a)pyrene concentrations of 2-1,000 mg/m³ were found in effluents from coking and petrochemical plants. The PAH content in drinking water can be reduced by ozonation, chlorination, and UV irradiation. (321 refs)

- 79-1233 Some Aspects on the Dosimetry of the Carcinogenic Potency of Asbestos and Other Fibrous Dusts.** (Eng) Pott, F. (Dusseldorf, W. Germany). *Staub-Reinhalt Luft* 38(12): 486-490; 1978.

Factors related to the dosimetry of carcinogenic fibrous dusts are discussed. Length and diameter are among the most important factors related to the dosimetry of fiber carcinogenicity. It is hypothesized that there exists a gradual transition from the noncarcinogenic fiber length or diameter to the fiber length or diameter that possesses max fiber carcinogenicity. In studies in which rats were injected ip with 13 different fibrous dusts, tumor incidence depended on the fiber number in most cases. However, with milled chrysotile A, there was no obvious correlation with fiber number and there was an overall low incidence of tumors with no asbestosis. Human studies have also shown that asbestosis is not a necessary predisposing condition for carcinogenicity, indicating that asbestosis is caused by fibers of different sizes than those that cause tumors or that tumor induction requires fewer fibers than those that cause asbestosis. Other than fiber length and diameter, aerodynamic diameter, irregularities in form, solubility, and the possibility of splitting or breaking should be considered in evaluating fiber carcinogenicity. (27 refs)

- 79-1234 Dust Diseases of the Lungs: Part 2.** (Eng) Longley, E. O. (Worker's Compensation Board--Dust

Diseases, Sydney, Australia). *Med J Aust* 2(10): 474-476; 1978.

Information concerning asbestosis and byssinosis is reviewed. The discussion of asbestosis includes pleural plaque formation and calcification, symptoms and signs, radiological changes, differential diagnosis, and the relationship between asbestosis and bronchogenic carcinoma, mesothelioma, and desquamative interstitial pneumonitis. Byssinosis is characterized by dyspnea and chronic cough associated with cotton flax and hemp occupations. Its diagnosis is discussed. (1 ref)

- 79-1235 Underground Mines and Diesels--The Health and Safety Aspects.** (Eng) Wenberg, R. V. (No affiliation given). *Am Min Congr J* 65(1): 21-25; 1979.

Cancer risk in persons who work in mines in which diesel equipment is used is discussed. No data implicating diesel exhaust as a carcinogenic agent in humans or animals exist. Numerous studies have shown that the levels of NO₂ found in mines in which diesel equipment is used are <5 ppm, the current government standard. (4 refs)

- 79-1236 The Relation of Repair Phenomena to Mutation Induction in Bacteria.** (Eng) Kimball, R. F. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830). *Mutat Res* 55(2): 85-120; 1978.

The role of enzyme systems involved in DNA repair, replication, and recombination in the induction of mutations in bacteria by physical and chemical agents is reviewed. Many enzymatic processes can repair potentially lethal or mutagenic lesions in DNA before these lesions can be converted to final mutations. These processes range in complexity from simple reunion of strand breaks by DNA ligase to multistep processes such as those involved in the excision of pyrimidine dimers. Repair can also remove potentially lethal lesions at the expense of creating premutational lesions or final mutations. A number of mutagens, including UV light, ionizing radiation, and several chemicals, induce an error-prone process, perhaps a modification of the proofreading system, that allows bacteria to survive after potentially lethal damage at the expense of making errors. Some mutagens, notably, monofunctional alkylating agents and base analogs, produce mutations by other processes. Even in these cases, repair processes play an important role. There is some evidence that error-free as well as error-prone repair processes can be induced. For example, growth of bacteria in the presence of low concentrations of alkylating agents can cause resistance to the lethal and mutagenic effects of high-concentration, acute exposures. The relation of these findings to the practical problem of hazards estimations is discussed. (244 refs)

- 79-1237 Replication of Chemically Modified DNA.** (Eng) Villani, G. (Departement de Biologie Moleculaire, Universite Libre de Bruxelles, B-1640 Rhode

St., Genese, Belgium); Spadari, S.; Boiteux, S.; Defais, M.; Caillet-Fauquet, P.; Radman, M. *Biochimie* 60(10): 1145-1150; 1978.

A hypothesis concerning the replication of chemically modified DNA and its relation to mutagenesis is proposed based on a number of published studies. The data indicate that UV photo-products, probably pyrimidine dimers, block, at least temporarily, the continuous progress of the DNA replication complex in bacteria and in mammalian cells. The dose response of the inhibition of DNA synthesis suggests that each pyrimidine dimer is both an absolute block to polynucleotide chain elongation in vitro and a lethal hit in vivo. A 3' to 5' exonuclease has been purified that can arrest DNA synthesis by purified α polymerase on damaged templates. It is hypothesized that this exonuclease is a true proofreading exonuclease with biological functions analogous to those of the polymerase-associated 3' to 5' exonuclease of *Escherichia coli*. Recent findings that mutagenesis of both intact and UV-irradiated herpesvirus can be triggered by UV irradiation of the host cell support the idea that induced mutagenesis in mammalian cells could be a genetically controlled process involving the activity of the proofreading exonuclease. (41 refs)

79-1238 DNA Repair Defects in Genetic Diseases in Man. (Eng) Bootsma, D. (Dept. Cell Biology and Genetics, Erasmus Univ., Rotterdam, Netherlands). *Biochimie* 60(10): 1173-1174; 1978.

Several genetic diseases are associated with defects in DNA repair. The mutation in xeroderma pigmentosum affects an excision repair process involved in the removal of UV-induced pyrimidine dimers. A reduced rate of excision of γ -ray-induced DNA base lesions has been observed in a large number of ataxia telangiectasia patients. In Fanconi's anemia, a defect in repair of DNA interstrand crosslinks and closely spaced overlapping damage is indicated. Bloom's syndrome, although showing a high rate of sister chromatid exchange, has not been shown to be defective in DNA repair. (16 refs)

79-1239 Sun, Light and Human Health. (Eng) Henderson, J. S. (Dept. Pathology, Faculty Medicine, Univ. Manitoba, Winnipeg, Manitoba, Canada R3E 0W3); Jenks, I. H. *Photochem Photobiol* 29(1): 1-5; 1979.

The relationship between sunlight and various diseases, including skin cancer, lupus erythematosus, and the porphyrias, is surveyed briefly, along with interactions between sunlight and the ozone layer and between sunlight and air pollution. (no refs)

79-1240 What Is the Misunderstanding All About (3 Letters to Editor)? (Eng) Cohen, B. L. (No affiliation given); Morgan, K. Z.; Rotblat, J. *Bull At Sci* 35(2): 53-59; 1979.

Two previous articles indicating that the carcinogenicity of low-level radiation is much higher than had been previously believed are criticized, and the authors' responses are presented. (7 refs)

79-1241 Adult Leukemia Following Diagnostic X-Rays? (Eng) Boice, J. D. (Environmental Epidemiology Branch, NCI, Room 3C-07, Landow Building, Bethesda, MD, 20014); Land, C. E. *Am J Public Health* 69(2): 137-145; 1979.

A recent study (by Bross et al) employing a new statistical methodology to reanalyze data from a tristate (New York, Maryland, and Minnesota) leukemia study is reviewed. The Bross report indicated that adult leukemia was related to diagnostic x-ray skin doses between 0.1 and 10 rads, and that previous risk estimates underestimate radiation hazards by a factor of 10. It is felt that the conclusion of the article (that a dose-effect curve was demonstrated in the 1-rad range) is not justified by the analysis or data reported. Although other studies have reported a possible association between a small percentage of adult myeloid leukemia and diagnostic radiation, the risk of myeloid leukemia appeared to be concentrated among subjects receiving unusually large numbers of examinations, and the association may have been indirect rather than causal. The results of radiation-induced leukemia studies and studies referenced by Bross are controversial with respect to interpretation. The Bross paper stretched the data far beyond reasonable limits to produce unwarranted conclusions. The new statistical methodology used in the study depended on a model that was far too complex to be useful. It is doubtful that the model was a reasonable representation of the relationship between radiation dose and leukemia risk. Furthermore, in contrast to the interpretation of Bross et al, the shape of the purported dose-response curve implies that low-dose radiation has less effect per rad than high-dose radiation and that linearity overestimates the risk of radiation exposure at low doses. In conclusion, the Bross et al analysis does not indicate that the risk of low-level radiation exposure is greater than that currently accepted. (69 refs)

79-1242 The Hazards of Fallout or of Epidemiologic Research? (Eng) Land, C. E. (NCI, Bethesda, MD, 20014). *N Engl J Med* 300(8): 431-432; 1979.

The results of a recent study indicating an increased risk of leukemia in children born in "high fallout" rural Utah counties during the period of active nuclear weapon testing must be interpreted carefully. Not only was the control group chosen from different time periods, but it was drawn from "low fallout" counties that are largely urban. Furthermore, mortality for these same high-risk children from cancers other than leukemia is inordinately low, suggesting the possibility of a purely fortuitous association. (3 refs)

79-1243 Recurrent Osteoblastoma: A Review. (Eng) Jackson, R. P. (Dept. Surgery, Univ. Kansas Medical Center Coll. Health Sciences and Hosp., 39th and Rainbow Blvd., Kansas City, KS, 66103). *Clin Orthop* (131): 229-233; 1978.

Three new and 181 previously reported osteoblastomas are reviewed. Eighteen recurrences were found in the 184 cases, more commonly in the spine and pelvis than in other sites. Recurrences were reported as long as 9 yr after excision, indicating the need for long-term follow-up of this lesion. No recurrence has been reported after complete en block resection. Postoperative irradiation does not appear to prevent recurrence of incompletely excised lesions. Five of the recurrences underwent apparent sarcomatous change. In 3/5 sarcomas, the period from initial treatment to diagnosis of malignancy was 6-10 yr; this information was not given in the other two cases. Four of the five sarcomas developed in patients who had received radiotherapy after incomplete excisions. The other sarcoma developed in a patient who had not been irradiated. These results indicate that radiotherapy is not effective in preventing recurrence of osteoblastoma and may possibly be associated with late sarcomatous change in some cases. (14 refs)

79-1244 Ionizing Radiation and Human Breast Cancer. (Eng) Feig, S. A. (Dept. Radiology, Thomas Jefferson Univ. Hosp., Philadelphia, PA). *CRC Crit Rev Diagn Imaging* 11(2): 145-166; 1978.

Epidemiological studies of radiation-related breast cancers in women are reviewed. Four groups of women were included in the studies: (1) Japanese women exposed to atomic bomb gamma; (2) women from Rochester, New York, treated with radiation for postpartum mastitis; (3) Nova Scotia, New England, and Toronto sanatoria patients subjected to multiple chest fluoroscopies; and (4) Swedish women treated with radiotherapy for nonmalignant breast conditions. In each of these series, there was a higher than expected number of women who developed breast cancer. The cancer developed at an earlier age than in nonirradiated women. In cases in which only one breast was irradiated, there was a correspondence between the irradiated side and subsequent development of breast cancer. The breast cancer incidence rate showed a striking dependence on age of the patient at first irradiation. Generally, women irradiated at ≤ 30 yr of age had a significantly increased risk of breast cancer. In the Group 2 women, however, irradiation postpartum after age 30 did not confer an absolute breast cancer risk substantially different from that seen in women irradiated prior to age 30. It is suggested that full-term pregnancy returns the breast to an earlier, more sensitive physiologic state. (40 refs)

79-1245 Radiation and the Induction of Malignancy. (Eng) Hazel, J. J. (Dept. Therapeutic Radiology, Royal Victoria Hosp., Montreal, Quebec H3A 1A1, Canada). *Clin Nucl Med* 4(2): 84-85; 1979.

Information concerning radiation-induced (R-I) malignancies is reviewed briefly. The topics covered include the pathogenesis of R-I tumors, pathogenesis, body areas susceptible to R-I carcinogenesis, significance of radiation dose, and the prognosis of R-I malignancies. (14 refs)

79-1246 The Role of X-Ray Pelvimetry in Modern Obstetrics. (Eng) Granados, J. L. (No affiliation given); Haskins, A. L.; Lahom, L. R. *Bull Univ Md Sch Med* 63(4): 4-8; 1978.

The hazards to the fetus of low-level radiation, the advantages and limitations of pelvimetry during pregnancy, and the correlation of x-ray pelvimetry to obstetrical outcome are reviewed. The literature suggests that leukemia and possibly other neoplasms and other major causes of death in childhood may be induced by in utero exposure to low-level radiation. (16 refs)

79-1247 Micronesia: America's "Strategic" Trust. (Eng) Johnson, G. (No affiliation given). *Bull At Sci* 35(2): 10-15; 1979.

The medical and sociological consequences of US nuclear bomb testing in the Marshall Islands in the 1940's and 1950's are discussed. Since 1964, > 90% of the children on one atoll, Rongelap, who were < 12 yr old at the time of an explosion in 1954 have developed thyroid tumors. A total of 40% of all exposed Rongelapese have developed thyroid problems. Although the Atomic Energy Commission told inhabitants of a neighboring island, Utirik, that the 14 rads of radiation they had experienced was harmless, 11 thyroid tumors were observed among 157 islanders over 23 yr; in addition, there was a sharp increase in the thyroid disease and cancer rate among the Utirikese in 1977. (13 refs)

79-1248 Genetic Aspects of Carcinogenesis and Carcinogen Testing. (Eng) O'Brien, S. J. (Immunology Section, Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD, 20014); Rice, M. C. *J Toxicol Environ Health* 5(1): 69-81; 1979.

Studies of mammalian cellular genes as targets of carcinogens are reviewed, and the question of inbred vs outbred mice as a model system for human carcinogenesis is considered. More than 30 genes that participate in the generation of leukemias, sarcomas, and carcinomas have been studied in human, mouse, and cat systems in vivo and in vitro. Seventeen of these genes have been localized to a specific chromosome in the particular species, and the rest are being mapped. Three classes of genes have been studied as they are related to tumorigenesis: (1) those controlling the expression of in vitro tissue culture correlates to malignant transformation; (2) those involved in the enzymatic activation of carcinogens; and (3) those related to the replication and expression of endogenous C- and B-type RNA tumor viruses or retroviruses.

Cellular genes that regulate the expression of these viruses are likely chromosomal targets of carcinogens. Three laboratory populations of outbred Swiss-Webster mice were tested for a number of gene-enzyme systems that would electrophoretically resolve the nature and extent of genetic variation. The frequency of polymorphic loci was slightly less than that in wild mice or in humans, but the av heterozygosity was indistinguishable from published estimates for mouse and human. It is concluded that Swiss mice are genetically as well as functionally outbred. (59 refs)

- 79-1249 Structure, Replication, and Recombination of Retrovirus Genomes: Some Unifying Hypotheses.** (Eng) Coffin, J. M. (Dept. Molecular Biology and Microbiology, Tufts Univ. Sch. Medicine, 136 Harrison Ave., Boston, MA, 02111). *J Gen Virol* 42(1): 1-26; 1979.

Structural features of the retrovirus genome and mechanisms for its replication and recombination are reviewed. Retroviruses use a system different from that used by all other known virus groups to ensure that all portions of the genome are copied into double-stranded DNA. The system combines direct terminal repeats in the genome and the ability of the polymerase to move, along with the nascent chain, from one template to another. The mechanisms that relate one proviral DNA structure with another are not yet fully understood. The absence of specific integration sites and the presence of additional information at each end of the integrated provirus suggest that control sequences for initiation and, possibly, termination of virus RNA synthesis are encoded in the virus genome. A model for recombination by breakage repair is proposed. The key assumption is that when a polymerase molecule encounters a break in the template, it behaves the same way as it does when it reaches the end of an RNA template. Thus, the polymerase halts and the template is subsequently degraded by RNase H. This frees the nascent chain for base-pairing, but this time with the corresponding sequence on the other molecule in the dimer. If another break is encountered in the course of subsequent synthesis, the growing chain will be transferred back to the first template and so forth, leading finally to a recombinant virus. (122 refs)

- 79-1250 Type-C Oncornaviruses and Autoimmunity.** (Eng) August, J. T. (Dept. Pharmacology, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205); Strand, M. *Arthritis Rheum* 20(6, Suppl): S64-S73; 1978.

The participation of an endogenous viral gene in the autoimmune disease of New Zealand Black (NZB) mice is discussed. The viral component most strongly implicated is the 70,000-dalton envelope glycoprotein of an endogenous murine C-type oncornavirus. This glycoprotein is expressed in the cells of all mice independently of the synthesis of virions or other viral proteins. It is found on cell membranes as a viral cell-surface antigen and is also found in serum. In NZB mice, the concentration of glycoprotein in cells and serum is higher than that in other strains, and in some reticuloendo-

thelial and epithelial cells it is a major cell protein constituent. Evidence indicates that the mice are not immunologically tolerant to the glycoprotein and that immune complex deposition occurs in the kidneys of both NZB mice and aging mice of other strains. Several genes appear to be involved in NZB autoimmune disease, and the presence of high concentrations of virus gene product alone is insufficient to induce it. There is no clear evidence as to whether or not the endogenous virus is a necessary factor or one of several factors that can influence the disease process in an appropriate host. (63 refs)

- 79-1251 Biosynthesis of Murine Leukemia Virus Membrane Proteins and Their Assembly into Virus Particles.** (Eng) Arlinghaus, R. B. (Biology Dept., Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Murphy, E. C.; Naso, R. B.; Arcement, L. J.; Karshin, W. L. *ACS Symp Ser* 80: 180-200; 1978.

Events leading to the formation of mature viral envelope proteins and their assembly into virions are summarized. In addition, a model for virion assembly and budding of the virus particle from the cell is proposed. Topics discussed include the virion proteins of Rauscher murine leukemia virus (R-MuLV), intracellular viral specific glycoproteins, presence of gp69/71 and p15(E) peptide sequences in gPr90-env, the gene order of the proteins within gPr90-env, viral protein p12(E), cell-free synthesis of an unglycosylated precursor to gp69/71 and p15(E), peptide maps of the envelope-related protein synthesized from intracellular 20S-22S messenger RNA, and translation of fractionated R-MuLV genomic RNA. These studies and those of others indicate that there are at least two size classes of messenger RNA's that code for R-MuLV proteins. A smaller size class of messenger RNA (approx 22S) apparently codes for the envelope proteins. A model for the synthesis and processing of R-MuLV proteins is described. According to the virus-assembly model, cleavages of Pr65-gag and Pr200-gag-pol are probably required for virus budding and release. However, it is possible that Pr65-gag and Pr200-gag-pol may be cleaved not during budding but after release of virus from the cell. (62 refs)

- 79-1252 Fucosylation--A Role in Cell Function.** (Eng) Glick, M. C. (Dept. Pediatrics, Univ. Pennsylvania Medical Sch., Children's Hosp. Philadelphia, Philadelphia, PA, 19104). *ACS Symposium Series* 80: 404-411; 1978.

The fucose (FC)-containing glycopeptides of the membranes of virus-transformed and tumor cells are different from those of normal cells: the glycopeptides are more highly branched on the virus-transformed cells. Although FC served as a radioactive marker to detect these differences, no difference has been found in FC per se. The similarities of FC among several cell types and some unique properties of FC in mammalian glycoproteins are summarized and used to suggest that FC may play a special role in the relationship of the surface mem-

brane to the cell. Three observations are directly suggestive of a role for FC: (1) most membrane glycoproteins are fucosylated; (2) FC is positioned near the glycopeptide core; and (3) α -L-fucosidase activity is not significantly elevated after virus transformation. Furthermore, FC is the only monosaccharide that occurs as an L-isomer and a deoxy sugar but never as the N-acetyl derivative, which suggests that FC may be in a unique position because of its structure alone. Relatively large amounts of two unusual components are associated with the surface membrane containing FC. One is the major high-mol-wt glycoprotein excreted by human fibroblasts in culture, and the other is a low-mol-wt component of the cell surface. Finally, FC found in the membrane glycoproteins shows two different rates of acid hydrolysis and two different specific activities. The use of cell-surface variants defective in membrane glycoproteins may be useful in ascertaining the special role that FC may have in the relationship of the surface membrane to the cell. (21 refs)

- 79-1253 The Stabilization of Cell Lines by Viruses.** (Eng) Harnden, D. G. (Dept. Cancer Studies, Univ. Birmingham Medical Sch., Birmingham, England 11). *Prog Clin Biol Res* 26: 11-23; 1978.

The stabilization of cell lines by viruses is discussed. Only a limited number of viruses can alter cells in such a way that they develop into established lines. Among the RNA viruses, only the oncogenic members of the retrovirus group with a C-type morphology can bring about cellular transformation, whereas oncogenic members of all main groups of DNA viruses can do so. A cell infected by an RNA virus may be both transformed and virus-producing, whereas DNA viruses will cause only lytic infections in some cell types and only transformation in others. The transformed cell lines will have unique combinations of the characteristics typical of the transformed phenotype, even when they are induced by the same virus. Viral transformation appears to be necessary but not sufficient for creation of a population of malignant cells or malignant tumor development in vivo. The possibility of generating cell lines altered by a virus but not having a classical transformed phenotype should not be overlooked. (19 refs)

- 79-1254 Herpes Simplex Virus Infections.** (Eng) Felman, Y. M. (Bureau Venereal Disease Control, City New York Dept. Health, New York, NY); Sonnabend, J. A. *NY State J Med* 79(2): 179-185; 1979.

The association of herpes simplex virus (HSV) with cervical cancer (CC) is discussed in this review of HSV infections. Cervical dysplasia, carcinoma in situ, and invasive cervical carcinoma are associated with HSV type 2. However, just as women with genital herpes, associated with HSV type 1 or type 2, may not develop CC, CC can occur in women with no evidence of HSV. Herpesviruses have been shown to transform cells in vitro and to have oncogenic effects in experimental animals. (52 refs)

- 79-1255 Etiology of Lymphomas and Leukemias: Role of C-Type RNA Viruses.** (Eng) Kaplan, H. S. (Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305). *Leuk Res* 2(4): 253-271; 1978.

The role of C-type RNA viruses in the induction of lymphomas and leukemias is reviewed. Leukemogenic viruses have been isolated from lymphomas and lymphatic leukemias of murine, feline, bovine, Syrian hamster, and subhuman primate origin. Purified RNA tumor virus particles contain RNA-dependent DNA polymerase, reverse transcriptase (RT), which can synthesize complementary DNA from viral RNA templates. The RT's extracted from RNA tumor viruses of different mammalian species can be distinguished immunologically. The viral genome contains four genes, but sequences specifically associated with leukemogenic activity have not yet been identified. The feline, bovine, and gibbon ape leukemia viruses have all proved to be exogenous, horizontally transmitted C-type RNA viruses. The leukemogenic viruses are remarkably selective with respect to the types of target cells they transform. Three classes of antigens have been identified: virion, cell-surface, and soluble antigens. Acute myeloid leukemias were the first reported human source of C-type RNA viral isolates. At least 8/15 cell lines, representing 3 different types of malignant lymphomas, have spontaneously initiated the sustained production of C-type RNA viruses. Normal human peripheral blood and bone marrow cells infected with one of these viruses (DHL-1) have shown changes in their growth behavior and morphology, but these responses have not been sustained. Immunological studies suggest that the RT of DHL-1 virus is unrelated to that of the murine and feline C-type viruses, but is remotely related to the enzyme of subhuman viruses. (296 refs)

- 79-1256 Viral Infections of the Vulva.** (Eng) Josey, W. E. (Emory Univ. Sch. Medicine, Atlanta, GA). *Clin Obstet Gynecol* 21(4): 1053-1059; 1978.

Vulvar infection with herpes simplex viruses types 1 and 2 (HSV-1 and HSV-2) is reviewed. Although a causal role for herpes viruses in human cancers has not been proved, the ability of human herpes viruses to cause neoplastic transformation in tissue culture or in experimental animals has been demonstrated conclusively. HSV-1 infections are chiefly acquired in childhood, and HSV-2 infections occur mainly in adults. HSV-1 is associated primarily with nongenital herpetic infections, HSV-2 with genital herpetic disease. However, 10% of genital infections are caused by HSV-1. In the genitals, HSV-2 infection commonly involves the cervix as well as the vulva, whereas HSV-1 infection is more likely to be confined to the external genitalia and tends to be more superficial than type 2 lesions. Although considerable seroepidemiologic and experimental evidence supports the theory that HSV-2 infection may be etiologically related to carcinoma of the cervix, present information on a possible relation to cancer of the vulva is scanty. There is an association of some vulvar carcinomas with carcinoma of the cervix, suggesting

that the same etiologic factors may be operative in both cancers. There have been reports of cases of marked intraepithelial vulvar atypia approaching carcinoma in situ, occurring as a sequel to HSV-2 vulvitis during pregnancy, that have reverted to normal in the postpartum state. These cases suggest a possible carcinogenic effect of HSV-2 on the vulva under appropriate conditions of host susceptibility. (8 refs)

79-1257 Cutaneous Manifestations Occurring Systemically in Heritable Forms of Colon Cancer. (Eng)

Kopelovich, L. (Memorial Sloan-Kettering Cancer Center, Cornell Univ. Graduate Sch. Medical Sciences, New York, NY, 10021). *Monogr Hum Genet* 10: 156-164; 1978.

Skin fibroblasts from patients with adenomatosis of the colon and rectum (ACR) are defective in growth control and cytoplasmic organization and are differentially transformed by an RNA oncogenic virus. These phenotypic disorders are likely to be systemic and may be related to the presence of early and previously undetected biochemical lesions in skin fibroblasts from ACR genotypes. (49 refs)

79-1258 Immunological Surveillance Against Neoplasia: An Immunological Quandary. (Eng) Drew, S. I.

(Dept. Medicine, Univ. California Sch. Medicine, Los Angeles, CA, 90024). *Hum Pathol* 10(1): 5-14; 1979.

Arguments for and against the theory of immunological surveillance (IS) against neoplasia are reviewed. The IS hypothesis proposes that there is an immunological system capable of recognizing tumor cells as "nonself" and aborting the growth of aberrant cells in the early stage of tumor development. Evidence of tumor induction in immunosuppressed animals challenged with carcinogens and the demonstration of an immune response to tumors in animals support the hypothesis. The concept has also found support in the clinical situation, in which tumor incidence in immunosuppressed individuals is notably increased. The occurrence of tumor, regarded as a failure of IS, is attributed to selection of neoplastic cells for immunological or other reasons or abnormal humoral or cellular antitumor immune responses. However, the monoclonality of certain tumors (multiple myeloma, chronic lymphatic leukemia, Waldenstrom's macroglobulinemia, chronic lymphosarcoma-leukemia, and Burkitt's lymphoma) and the low incidence of spontaneous tumors in genetically immunodeficient mice and immunologically privileged sites argue against the IS hypothesis. On the basis of current evidence, the relationship between spontaneously arising tumors and the immune system may be envisaged as follows: (1) the existence of an IS system as an entity independent of the normal antitumor immune response is a redundant concept; (2) spontaneous neoplastic transformation is a rare in vivo event; (3) therefore, in view of 1 and 2, there is no need for IS; and (4) tumors elicit an immune response, which in most cases fails to intercept tumor growth. (63 refs)

79-1259 The Pathogenesis of Hodgkin's Disease. (Eng) Stuart, A. E. (Dept. Pathology, Univ. Newcastle upon Tyne, Tyne NE1 4LP, England). *J Pathol* 126(4): 239-254; 1978.

The histopathology of Hodgkin's disease (HD) is reviewed in relation to experimental findings. Serum immunoglobulins are increased in many patients with untreated HD, and serum factors that depress in vitro lymphocyte responses to mitogens, modify erythrocyte (E)-rosette-forming ability, or bind to T lymphocytes have been described. Lymphocytopenia often occurs in HD, and atypical lymphocytes have been repeatedly described, as has increased spontaneous DNA synthesis by blood T lymphocytes. The absolute number of T lymphocytes is often slightly reduced, and B cells may be raised in number. There seems to be a specific interaction between serum factors and the surface of peripheral T lymphocytes, and there is a distinct redistribution of T cells between blood, spleen, and lymph nodes. The Reed-Sternberg cells identified in patients with HD appear to be neoplastic, and it is likely that they are derived from a disordered B cell that matures through a sequence of mononuclear and polynuclear forms. The tendency for T lymphocytes to swarm around viable Reed-Sternberg cells appears to be an integral part of the HD process and may be significant in the evolution of the disease. The ecotaxis of T cells in HD is probably a reflection of this interaction between T lymphocytes and Reed-Sternberg cells. (99 refs)

79-1260 Membrane Biochemistry and Physiology of Human Colonic Cancer. (Eng) Freeman, H. J. (Veterans Admin. Hosp., San Francisco, CA); Kim, Y. S. *Cancer Bull* 30(6): 237-242; 1978.

Studies concerning the normal cell membrane and alterations in glycoproteins, glycolipids, cell-surface tumor antigens, and transport in colonic cancer are reviewed. Features that differentiate malignant from normal cells include the ability to grow and proliferate independently of normal control mechanisms, to invade normal tissues, and to metastasize to distant sites. Increasing evidence indicates that these characteristics are largely controlled or modulated by the tumor cell nucleus and surface membrane. Significant membrane alterations occur in colonic malignancy, and they include changes in certain blood group activities of membrane glycoproteins and glycolipids and expression of cell-surface membrane tumor antigens. Elucidation of the precise molecular basis for these cell-surface membrane alterations may lead to improved detection and treatment of colonic cancer. In addition to specific malignant alterations of membrane components, functional changes associated with malignant transformation include changes in membrane transport of certain nutrients. Increased transport of glucose, several glucose analogs, mannose, galactose, glucosamine, and various amino acids occurs with transformation. In general, V_{max} increases but K_m remains unchanged or is decreased. This suggests that the number of transport sites in carrier-mediated uptake is increased for various nutrients. Changes in membrane proteins in rela-

tion to the membrane uptake and transport of certain chemotherapeutic agents also appear to occur with neoplasia. (26 refs)

- 79-1261 Genitourinary Tumors and Immunology.** (Eng) Lange, P. H. (Minneapolis Veterans Admin. Hosp., Minneapolis, MN). *Proc Inst Med Chic* 32(4): 58-59; 1978.

Progress in the field of genitourinary tumor immunology is reviewed. Studies of immunotherapy have been carried out in patients with renal cell carcinoma, transitional cell carcinoma, and prostatic cancer, and the immunotherapeutic agents studied have included BCG, transfer factor, immune RNA, and serum cross transfusion. Several serological tumor markers have proved useful in the management of patients with testicular tumors. Another area of human tumor immunology is the detection and characterization of antigens on the tumor cell per se. (4 refs)

- 79-1262 Experimental Tumors of the Urinary System.** (Bul) Stoichev, I. (Lab. Chemical Carcinogenesis, Res. Inst. Oncology, Sofia, Bulgaria). *Onkologiya* 15(3): 148-155; 1978.

Data on chemically induced tumors of the urinary system are reviewed. Chemicals that induce urinary system tumors include aromatic amines, nitrosamines, nitrofurans, chemical compounds of natural origin (some antibiotics, aflatoxin, methylazoxymethanol acetate), and various metabolites. Histologically, the induced tumors are papillomas, adenomas, and carcinomas. (64 refs)

- 79-1263 Report of the Workshop on Mutagenicity.** (Eng) Roderick, T. H. (Jackson Lab., Bar Harbor, ME). *J Toxicol Environ Health* 5(1): 163-165; 1979.

Mammalian systems that are used to test transmissible mutagenic damage or that have direct relevance to transmissible effects were discussed at a mutagenicity workshop, and the findings are reviewed. The dominant lethal, translocation, specific locus, X-chromosome loss, unscheduled DNA synthesis, and sperm abnormality tests are described briefly. (no refs)

- 79-1264 Genetic Structure of Human Populations.** (Eng) Schull, W. J. (Center Demographic and Population Genetics, P.O. Box 20334, Houston, TX, 77025). *J Toxicol Environ Health* 5(1): 17-25; 1979.

The difficulties of extrapolating the toxicity responses of experimental organisms to humans are discussed. Contemporary methods of evaluation assume little heterogeneity among members of the human population in their response to a substance. However, measurement of enzymic variation reveals

that humans are more variable genetically than most mammalian species. In one study in which 10 mammalian species were examined, human heterozygosity values were two to six times greater than those of 2 primates (both macaques) and more than twice as great as those of most feral rodents represented. Evaluation of toxicological hazards should also consider responses to potentially toxic substances by individuals who carry rare genetic alleles. The effects of population structure (its system of mating and its effective size, as well as its patterns of reproduction, mortality, and migration) on genetic variability are also discussed. In contemporary human populations, migration rates are not sufficiently restricted and inbreeding and phenotypic assortative mating rates are not sufficiently large to play important roles in limiting genetic diversity. Hidden genetic variability in humans could be enormous, leading to much wider responsiveness to the toxic effects of environmental chemicals than presently appreciated. Seemingly harmless drugs or food additives (as judged from animals less diverse than humans) may, in fact, have serious toxic effects on a nontrivial number of humans because of the great genetic diversity present. (32 refs)

- 79-1265 Cancer Metastasis: A Product of Tumor-Host Interactions.** (Eng) Sugarbaker, E. V. (Dept. Surgery and Oncology, Univ. Miami, Miami, FL). In: *Curr Probl Cancer* 3(7): 1-59; 1979.

Clinical and experimental data on metastasis are reviewed extensively. A number of studies have demonstrated the systemic dissemination of cancer cells early in the course of certain malignancies. Cancer cells must complete three phases, entrance into a vascular conduit, transportation to a distant organ or lymph node, and lodging and growth at the distant site, before they can become metastases. Cell characteristics favoring metastasis are listed. In addition, the site and size as well as genetic characteristics of the primary tumor modulate metastasis. Despite the growing body of data demonstrating the presence of immunostimulation of certain phases of neoplastic growth and metastasis, other data implicate immune rejection in metastasis. Extensive macrophage infiltration into primary tumors has also suggested a modulating role of macrophages in metastasis. Large numbers of tumor cells are probably also destroyed by nonimmunologic and nonspecific means. Heterogeneity has recently been definitively demonstrated in tumor cell populations, indicating that the metastatic cell may be analogous to clonal selection of mutant subpopulations derived from a common progenitor for neoplastic progression. The stage of a malignant disease (size of primary, presence or absence of histologically identified positive regional nodes) is the dominant determinant in patient prognosis. (191 refs)

- 79-1266 Induced Chromosome Variation in Cultured Cell Populations.** (Eng) De Carli, L. (Istituto di Biologia, Facolta di Medicina, Universita, Milano, Italy 93); Larizza, L. *Prog Clin Biol Res* 26: 93-124; 1978.

Spontaneous and induced variations in chromosome number and structure in cultured cell populations are reviewed. Chromosome variability has been used as an alternative to genetic variation via sexual reproduction for genetic analyses and has been employed in gene localization studies and in studies of the dynamics of karyotypes in neoplastic cells. Chromosome changes occur spontaneously in culture as a result of duplication or distribution errors. They can be induced in mammalian cultured cells by a variety of physical and chemical agents, including classical mutagens (ie, ionizing radiation, chemical compounds), changes in temperature or ionic strength, c-mitotic agents, and the antifungal agent griseofulvin (GF). The pattern of chromosome variation induced by these agents resembles that observed during the transition from primary culture to permanent in vitro line, and it has been suggested that GF-induced chromosome variations might facilitate the establishment of a cell line in vitro. One of the most effective ways of activating the dynamics of chromosome complements in vitro is the somatic cross, which brings about the formation of combined chromosome sets. The cytogenic structure of a cell population can also be manipulated by treatment of cells with morphologically intact metaphase chromosomes. The partial hybridization resulting from the incorporation of mitotic chromosomes suggests that chromosome transplantation may be a new method for gene localization. It would not be subject to the restrictions imposed by the directional loss of chromosomes in interspecific hybrids. (62 refs)

- 79-1267 Ectopic Insulin and Occam's Razor: Reappraisal of the Riddle of Tumour Hypoglycaemia.** (Eng) Skrabanek, P. (Endocrine Unit, Mater Misericordiae Hosp., Dublin, Ireland); Powell, D. *Clin Endocrinol (Oxf)* 9(2): 141-154; 1978.

The concept of ectopic insulin (IL) production is challenged on the basis of a review of 120 literature cases on extrapancreatic tumors associated with hypoglycemia in which IL or IL-like activity was measured. None of the cases given in support of the concept of ectopic IL met two or more of the following five criteria of ectopic hormone production: (1) greater concentration of IL in tumor than in surrounding normal tissue; (2) immunohistochemical localization of IL in tumor; (3) normalization of IL and of blood glucose concentrations after tumor removal; (4) arteriovenous gradient of IL concentration across the tumor bed; and (5) IL production by tumor in vitro. Several of these cases had a carcinoid histology. A close association was also observed between some spindle-cell tumors and carcinoid tumors. It is stressed that hypoglycemia is quite common as a terminal manifestation of malignancy because of a variety of causes; ie, cachexia, malabsorption, and impaired liver function. Nonsuppressible IL-like activity (NSILA), consisting of a number of factors mimicking IL activity that compete with IL or pro-IL for membrane receptors and may cross-react in various assays, was detected in 5/7 patients with hypoglycemic tumors by one investigator but not confirmed by another. It is possible

that one or several of these substances may be responsible for extrapancreatic hypoglycemia. (123 refs)

- 79-1268 Radiological Techniques in the Examination of Patients with Headaches.** (Eng) Komar, N. N. (1601 N. Tucson Blvd., Bldg. 1, Tucson, AZ, 85716). *Med Clin North Am* 62(3): 585-620; 1978.

In the radiologic investigation of headache patients, the principal recommended procedures are plain film study (PF) of the skull, computed tomography (CT), echoencephalography, and radionuclide brain scanning, particularly the first two. Special procedures such as cerebral angiography, pneumoencephalography, and posterior fossa myelography are usually performed when one of the noninvasive studies indicates a structural lesion or when the patient has a complex clinical presentation. PF evidence and localization of a tumor may be found when the cranial vault is involved, such as with meningioma. Almost any tumor that metastasizes to bone may do so to the cranial vault. Erosion of the sella turcica is found in one-third of patients with brain tumor. Approx 15% of all intracranial neoplasms are meningiomas. The cardinal PF signs of this tumor are hyperostosis, increased calvarial vascularity, and tumor calcification. PF evidence of calcification can also be found in approx 10% of glioma patients. CT is accurate and cost-efficient in the work-up of an individual suspected of harboring a brain tumor. At clinical presentation, many intracranial lesions have produced a definite mass. Most tumors are of low tissue density, but a gradation of low through normal to high density has been demonstrated by CT. The mass may be solid or cystic, it may be surrounded by edema, and it may contain inherent neovascularity. Enhancement by iv contrast material has been shown in 60% of supra- and infratentorial tumors and, when present, is an accurate determination of the boundary between tumor and surrounding edema. Low-grade astrocytomas tend to cause little mass effect or tissue reaction and thus are difficult to detect. Lesions such as cerebellar astrocytoma, metastasis, ependymoma, medulloblastoma, hemangioblastoma, and meningioma may all show CT evidence of the mass and edema effect, and a significant number will show contrast enhancement. (30 refs)

- 79-1269 Headaches and Head Pains Associated with Diseases of the Ear, Nose, and Throat.** (Eng) Birt, D. (Dept. Otolaryngology, Sunnybrook Medical Center, 2075 Bayview Ave., Toronto, Ontario M4N 3M5, Canada). *Med Clin North Am* 62(3): 523-531; 1978.

The identification or elimination of malignant disease is the crux of many otolaryngology consultations. Pain is a common symptom of malignant disease. Among the sinuses, the antrum and ethmoid are the most common sites for neoplastic disease. Sinus cancer often presents late, as signs and symptoms may not occur until the neoplasm has escaped the sinus itself. A wide spectrum of neoplasms may involve the sphenoid sinus, including squamous carcinoma, adenoidcys-

tic carcinoma, lymphoma, chondroma, chondrosarcoma, craniopharyngioma, meningioma, pituitary tumor, and angiofibroma. These tumors may cause bone erosion and pressure on surrounding structures, with visual disturbance, proptosis, and ophthalmoplegia also common. Malignant disease of the ear is rare, but should be considered if pain begins in a chronic discharging ear. Nasopharyngeal carcinoma NPC shares with the sphenoid the ability to cause headache in various places and also pain deep to the ear. Other presenting features of NPC include enlarged upper cervical lymph nodes, unilateral serous otitis, and nasal symptoms, and any combination of nerve palsies. Although NPC is most common in the fifth decade of life, it occurs frequently in young adults, particularly those of Southern Chinese origin. It also occurs in children. Pain arising from malignant disease in the oropharynx, hypopharynx, and supraglottic larynx is usually described as a sore throat or pain in the throat on swallowing, and there may be some earache. Glottic laryngeal carcinoma is seldom painful in the absence of perichondritis. (4 refs)

- 79-1270 Pathology of the Ear: Selected Topics.** (Eng) Friedmann, I. (No affiliation given.). *Pathol Annu* 13(1): 363-410; 1978.

Inflammatory diseases and neoplasms of the ear are reviewed. Inflammatory diseases considered include epidermoid cholesteatoma, cholesterol granuloma, catarrhal or secretory otitis media, and tympanosclerosis. Nonhealing (malignant) external otitis occurs in elderly diabetic patients and is caused by *Pseudomonas pyocyanea*. Neoplasms of the ear are rare, with an estimated incidence of 0.006/1,000 persons. The most common malignant neoplasm of the ear is squamous cell carcinoma. The pinna is the site of both squamous and basal cell carcinoma; distant metastases from squamous carcinomas of the ear are uncommon. Malignant glandular neoplasms of the ear are mainly of ceruminous gland origin. The predominant morphologic types of ceruminoma have been classified as follows: ceruminous adenoma, ceruminous adenocarcinoma, pleomorphic adenoma (mixed tumor), and adenoid-cystic carcinoma or cribriform adenocarcinoma. Schwannoma of the auditory nerve accounts for about 8% of all intracranial tumors. It is seen most often in the third and fourth decades of life and frequently presents as a cerebellopontine angle tumor. Cerebral neoplasms that may affect the ear include meningiomas, gliomas, and glioblastomas. In addition to rhabdomyosarcoma, which is the most common sarcoma of the ear, fibrosarcoma, osteosarcoma, and chondrosarcoma may also occur. Paragangliomas, which arise from the jugular bulb or from the promontory, are difficult to diagnose as malignant or benign on a histological basis. There is little information about the frequency of metastases in the temporal bone. (186 refs)

- 79-1271 Odontogenic and "Fissural" Cysts of the Jaws.** (Eng) Gardner, D. G. (No affiliation given.); Sapp, J. P.; Wysocki, G. P. *Pathol Annu* 13(1): 177-200; 1978.

The incidence, location, differential diagnosis, and histology of odontogenic and fissural cysts of the jaws are reviewed. The odontogenic keratocyst is important because of its aggressive behavior, its marked tendency to recur after surgical removal, and its association with the basal cell nevus syndrome. Additional features of this syndrome are multiple basal cell carcinomas, often occurring at an early age, skeletal anomalies, and a lack of response to parathormone. The possibility of this syndrome should be considered in any patient in whom an odontogenic keratocyst is diagnosed. The most common cyst of the jaws, the radicular cyst, is of inflammatory origin and develops within a periapical granuloma. It is lined by stratified squamous epithelium that often exhibits marked proliferation into the underlying connective tissue, a feature that has occasionally led to consideration of the diagnosis of ameloblastoma. However, ameloblastomas do not develop in radicular cysts. Squamous cell carcinoma has been reported on rare occasions in these cysts. Ameloblastomas may develop in dentigerous cysts, a common odontogenic cyst that occurs around the crown of an unerupted tooth. Mucoepidermoid carcinomas have also been observed on rare occasions in continuity with the epithelial lining of odontogenic cysts. Fissural cysts are developmental cysts of the jaws that are not derived from odontogenic epithelium, and they include nasopalatine duct, globulomaxillary, nasolabial, and median palatal cysts. (31 refs)

- 79-1272 Bras, Breast Carcinoma, and Cryptorchid Testis (Letter to Editor).** (Eng) King, C. R. (Dept. Obstetrics and Gynecology, Kansas Univ. Medical Center, Kansas City, KS, 66103). *Lancet* 1(8106): 45; 1979.

A previous suggestion that breast temperature is implicated in the etiology of breast neoplasia is criticized. It is difficult, without measuring the temperature within the breast tissue itself, to propose that glandular breast tissue has been exposed to unnatural temperatures by the dictates of fashion. A second previous suggestion that the high cancer incidence in undescended testes is caused by glandular tissue overheating is also criticized. Evidence that a testis is cryptorchid because it is abnormal is summarized. (10 refs)

- 79-1273 Pathology of Early Squamous Cell Carcinoma of the Lung.** (Eng) Carter, D. (No affiliation given). *Pathol Annu* 13(1): 131-147; 1978.

The detection, localization, and morphology of the early stage of squamous cell carcinoma of the lung, ie, the time before the patient becomes symptomatic and before the lesion is evident on plain chest x-ray, are reviewed. These lesions can only be detected by cytologic examination of the sputum. The chest x-ray of patients with positive sputum should be reviewed for suspicious areas that might have been overlooked. If this is not the case, the only means of localization of a bronchial lesion is a meticulous study of the upper airway and then the tracheobronchial tree, using a flexible fiberoptic bronchoscope. In 20 patients with preclinical squa-

mous cell carcinoma, in situ carcinoma was present in all cases but invasive carcinoma was present in only 12. The distribution of invasive carcinoma suggests that these lesions usually arise in segmental bronchi. The in situ carcinoma begins in the surface epithelium, usually in a segmental bronchus, from which it may spread in several directions. It frequently spreads in a proximal direction to involve lobar bronchi. It may also spread from the surface to involve the submucosal glands, and it may extend deep to the bronchial cartilage rings prior to the time that invasion occurs. The proximity of the invasive cancer to the bronchial cartilage makes its detection on x-ray difficult. Four of the 20 patients showed evidence of multifocal disease, a rate that had been suggested by other studies. (25 refs)

- 79-1274 The Mechanism of Bronchial Carcinogenesis.** (Fre) Masse, R. (Laboratoire de toxicologie experimentale, Departement de protection, Commissariat a l'energie atomique, Institut de protection et de surete nucleaire, BP 561, 92542 Montrouge Cedex, France); Arnoux, B. *Rev Prat* 28(59): 4679-4685; 1978.

Most human bronchial cancers are induced by chemical carcinogens, and tobacco smoke inhalation is the dominant etiological factor. The first stage of carcinogenesis is cellular and leads to the genetic transformation of a line. This stage depends on the target cell's sensitivity and on an individual's predisposition to cancer. A tissular stage contributes to clonal regulation and local accumulation of carcinogens. Expression of the initial lesion depends on the host immune system. The various stages are strongly influenced by cofactors. (10 refs)

- 79-1275 Spectrum of Lung Cancer and Ectopic Hormones.** (Eng) Yesner, R. (No affiliation given). *Pathol Annu* 13(1): 217-240; 1978.

Studies of production of ectopic hormones in patients with lung cancer are reviewed. Clinical syndromes associated with ectopic hormone production occur in 10% of all patients with lung cancer. Small cell carcinomas, particularly the oat cell type, produce the most ACTH, but it is also produced in significant amounts by all other types. Two forms of ACTH have been identified: "little ACTH" (39-amino acid polypeptide), which is the predominant form in normal pituitary extracts, and "big ACTH," which is the major component in lung tumors. Small cell carcinomas also produce more antidiuretic hormone (ADH) and calcitonin than the other types. Parathyroid hormone is almost exclusively produced by squamous cell carcinoma. Human growth hormone (HGH) is chiefly produced by adenocarcinomas and large cell carcinomas. Because there is an association of hypertrophic pulmonary osteoarthropathy (HPOA) with acromegaly, there has been much interest in the observation that tumors causing HPOA may also secrete HGH. HPOA is associated predominantly with adenocarcinomas, to a lesser extent with squamous cell carcinomas, and not at all with small cell carcinomas. The glycoproteins are predominantly but not

exclusively associated with large cell carcinomas, some of the giant cell type. These findings suggest that the degree, rather than the kind of hormone secretion, may be associated with the level of tumor maturation. (109 refs)

- 79-1276 General Review: Liver and Oral Contraceptives.** (Fre) Rauber, G. (Nancy, France). *Ann Gastroenterol Hepatol (Paris)* 14(6): 405-414; 1978.

The literature on benign and malignant hepatic tumors attributed to the use of oral contraceptives is reviewed. The pathogenesis of the tumors is discussed. Clinical symptoms may appear slowly or abruptly. Treatment is always surgical, and the postoperative mortality is not negligible. Patients who survive surgery have a good prognosis. (69 refs)

- 79-1277 Balkan Nephropathy.** (Eng) Hall, P. W. (Dept. Medicine, Case Western Reserve Univ., Sch. Medicine, Cleveland Metropolitan Hosp., 3395 Scrawton Rd., Cleveland, OH); Dammin, G. J. *Nephron* 22(4/6): 281-300; 1978.

Literature concerning endemic Balkan nephropathy (BN), a chronic tubulointerstitial nephropathy, is reviewed. There is a high incidence of BN in geographically restricted areas of Bulgaria, Romania, and Yugoslavia. Evidence pointing to environmental rather than genetic factors is substantial. However, the disease often occurs among multiple family members. Predominant tubular abnormalities, including tubular proteinuria, are the earliest manifestations of BN. The tubular proteinuria persists and becomes more prominent with the development of clinically detectable disease. Although the nature of the initial renal lesion remains controversial, a tubulointerstitial lesion accompanied by marked concentric atrophy and fibrosis of the subcapsular cortex is present in patients with azotemia. The inner cortex is less involved than the outer cortex. There is a high frequency of papillary transitional cell carcinoma of the renal pelvis and ureter in the same geographical areas in which BN is prevalent. The data suggest that BN is a definite entity. (70 refs)

- 79-1278 Germ Cell Tumors of the Ovary.** (Eng) Kurman, R. J. (No affiliation given.); Norris, H. J. *Pathol Annu* 13(1): 291-325; 1978.

Specific ovarian germ cell tumors are defined, and their diagnosis, behavior, and therapy are discussed. Benign cystic teratomas, about 1% of which become malignant, are the most common ovarian tumors, accounting for 14%-19% of all neoplasms at this site. Struma ovarii are teratoid tumors in which thyroid tissue represents more than half of the tumor component. A diagnosis of carcinoma has been made in 5% of struma ovarii, but metastasis has been reported in less than half of these; in many cases, the carcinomas in struma ovarii are not truly malignant. Carcinoid and strumal carcinoid tumors are also found in the ovary. Primary carcinoids

have not been known to metastasize; and there has been only one report of malignant behavior of a strumal carcinoid. The most common malignant ovarian germ cell tumor is dysgerminoma, followed by endodermal sinus tumor. However, dysgerminomas are rare, comprising only 2.5% of ovarian tumors. The majority of the patients are 10-30 yr old. Immature (malignant) teratoma is composed of variable amounts of immature tissue derived from any or all of the three germ layers, and it accounts for 1% of teratomas. It is frequently found in children. The malignancy of immature teratoma is related to its clinical stage and histologic immaturity. Endodermal sinus tumor occurs more frequently than pure immature teratoma. The patients range from age 14 mo to 45 yr. The tumor has an extremely rapid growth, with half of the patients presenting with symptoms of 7-day duration or less. Other malignant ovarian germ cell tumors include embryonal carcinoma (5%), choriocarcinoma, and mixed germ cell tumors (8%). (100 refs)

- 79-1279 Cutaneous and Vulvar Melanoma: An Update.** (Eng) Silvers, D. N. (Columbia Univ. Coll. Physicians and Surgeons, New York, NY); Halperin, A. J. *Clin Obstet Gynecol* 21(4): 1117-1133; 1978.

The diagnosis and treatment of cutaneous melanoma (CM) are reviewed with emphasis on vulvar melanoma. Most primary CM's have an in situ or superficially invasive phase of at least several years, during which time the tumor extends in a radial rather than vertical direction. Lentigo malignant melanoma, which accounts for 10% of all CM's, is rarely seen in the perineal region since it develops only on sun-exposed skin. Superficial spreading melanoma, which accounts for 80% of all CM's, can closely mimic a benign melanocytic nevus in its early invasive phase. However, after it has reached a diameter of >1 cm, it has characteristic clinical features, including an irregular, jagged border and a spectrum of colors. Nodular melanoma, which represents 10% of all CM's, does not have a clinically identifiable in situ phase, and by the time it has caused suspicion, it has already invaded to a depth suggestive of a poor prognosis. Follow-up studies of patients with primary CM have demonstrated that tumor thickness at the time of excision is closely correlated with prognosis. Melanoma accounts for 8%-11% of all invasive malignancies of the vulva. In 11 series totaling 352 cases, most lesions arose on the mucous membrane portion, specifically the labia minora and the clitoris. (34 refs)

- 79-1280 Vulvar Dystrophies.** (Eng) Kaufman, R. H. (Baylor Coll. Medicine, Houston, TX); Gardner, H. L. *Clin Obstet Gynecol* 21(4): 1081-1106; 1978.

Studies of vulvar dystrophies and of their significance with regard to malignant potential are reviewed. Most hyperplastic lesions previously called leukoplakia represent examples of lichen simplex chronicus (neurodermatitis). Vulvar dystrophies that exhibit atypical epithelial hyperplasia (dysplasia) are far more significant with regard to malignant potential

than benign epithelial hyperplasias. Most of these lesions are well-localized, delineated, slightly elevated, white, and rough. In lichen sclerosus, the skin has a crinkled parchmentlike appearance. Lichen sclerosus is often associated with both foci of hyperplastic epithelium and atrophic changes. The likelihood that a superimposed vulvar carcinoma will develop in a patient with chronic vulvar dystrophy is small, ranging from 1% to 5% over a long period. The patient who is probably destined to develop cancer is the one with microscopically proved atypical hyperplasia at the initial examination. In the absence of atypia in the dystrophic lesion, the danger of a subsequent carcinoma is almost nil. However, any chronic irritation of the vulva will add to the risk of carcinoma. (40 refs)

- 79-1281 Current Concepts of the Aetiology, Pathogenesis and Pathology of Bladder Cancer.** (Eng) Friedell, G. H. (Dept. Pathology, St. Vincent Hosp., Worcester, MA). *Urol Res* 6(4): 179-182; 1978.

More than one chemical carcinogen or combinations of chemical and biological agents may be involved in the etiology of bladder cancer (BC). In the US, most BC's are transitional cell carcinomas. Regardless of etiology, the pathogenesis of human BC appears comparable to carcinoma of the uterine cervix, bronchus, or oral cavity. Preneoplastic lesions, an experimental model for bladder carcinogenesis, irreversible epithelial hyperplasia, and the cellular characteristics of human BC are discussed. (19 refs)

- 79-1282 Nutritional Considerations in Colon Cancer Kinetics.** (Eng) Stragand, J. J. (Dept. Lab. Medicine, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX). *Cancer Bull* 30(6): 232-236; 1978.

Studies concerning the relationship between nutrition and intestinal cell and colon cancer cell kinetics are reviewed. Several studies have shown that dietary composition can produce distinct growth kinetic changes in the intestine and that the development of a malignant colonic lesion is preceded by a pattern of cell kinetics events that appear in both humans and experimental animals. Other studies have shown that the nutritional status of the host can markedly influence the growth kinetics of spontaneous and transplantable tumors in experimental animals. Studies of the cell kinetics of human colonic lesions have indicated that the overall production of cells is greater in the surrounding normal mucosa than in the tumor itself, which indicates that treating most colonic lesions with cycle-active antiproliferative agents could produce more damage in the coexisting normal tissue than in the targeted tumor cells. This indicates the need for a pretreatment strategy, possibly nutritional manipulation, that would be a nonspecific, tumor-synchronizing agent(s) with little or no normal tissue toxicity. Several theories concerning the etiology of large bowel cancer suggest the involvement of luminal carcinogens. The duration of exposure to these carcinogens

would be proportional to the intestinal turnover time. Because the presence of luminal material has been shown to stimulate cell production, a high-bulk diet might prevent the induction of cancer by reducing exposure to luminal carcinogens. (40 refs)

- 79-1283 Acute Scrotum.** (Ger) Rothenberger, K. (Urologischen Klinik, Städtisches Krankenhaus, Thalkirchner Strasse 48, 8000 Munich 2, W. Germany); Bowering, R. In: *National Cancer Week. Proceedings of the Annual Scientific Meeting held in Adelaide, Australia, 20-24 November 1978.* Clinical Oncological Society of Australia. 175 pp.; p. 170; 1979.

The differential diagnosis of diseases, including testicular tumors, that are manifested as acute scrotum (acute scrotal pain) are reviewed. (no refs)

- 79-1284 Methodology of the Study of Carcinogens in Human Populations.** (Eng) Shabad, L. M. (Dept. Carcinogenic Agents, Cancer Res. Center, Soviet Acad. Medical Sciences, Moscow, USSR). *J Toxicol Environ Health* 4(4): 637-643; 1978.

Primary approaches to study of the effects of chemical carcinogens on human health are epidemiologic and quantitative determinations of the effects of hazardous agents in different environments. Problems in determining max allowable concentrations of chemical carcinogens and extrapolating the findings to humans are also reviewed. (20 refs)

- 79-1285 Hereditary Cancer.** (Eng) Knudson, A. G. (Inst. Cancer Res., Philadelphia, PA). *JAMA* 241(3): 279; 1979.

A concurrently published article concerning a family with hereditary cancer is summarized briefly. Members who inherited the responsible dominant Mendelian gene had a high incidence of sarcomas, brain tumors, leukemias, and breast cancer, a nonrandom segment of the cancer spectrum. Other dominantly heritable neoplasias (ie, retinoblastoma, colon cancer associated with polyposis coli) show similar features. In many cases, the mutant genes have considerable specificity for one tumor or for a select tumor group. The mechanism of predisposition is not known for any of these dominantly inherited disorders. (1 ref)

- 79-1286 Methodologic Problems in Evaluating the Carcinogenic Risk of Environmental Agents.** (Eng) Strassburg, M. A. (County Los Angeles Dept. Health Services, Preventive/Public Health, Acute Communicable Disease Control, 313 N. Figueroa St., Los Angeles, CA, 90012); Greenland, S. *J Environ Health* 41(4): 214-217; 1979.

A paper that purported to prove a link between fluoridation of the water supply and cancer was evaluated to illustrate several pitfalls of data analysis that may occur in scientific papers. In evaluating any study of the relationship between cancer and potential carcinogens, several important points must be addressed: (1) exclusion of data may bias study results and should be carefully justified; (2) claims that a specific agent caused a change in death rates must be examined in terms of the rates both before and after exposure to the agent; and (3) in epidemiological observations, potential confounding variables must be considered. In the paper in question, these criteria were not followed. For example, three nonfluoridated cities were excluded from the study, and these three cities have cancer death rates that are 20%-27% higher than the national av. In addition, the fluoridated cities had the highest cancer death rates both before and after fluoridation was introduced. Industrialization may have been a confounding epidemiological factor, since the fluoridated cities are much more industrialized than the nonfluoridated ones. It is concluded that although the paper claims to have rallied impressive evidence linking cancer and fluoridation, it failed to provide evidence capable of withstanding careful scrutiny. This critique does not argue that fluoridation is safe or that it is not carcinogenic, but rather it presents scientific standards against which investigations should be judged. (6 refs)

- 79-1287 Epidemiology of Hemoblastoses.** (Rus) Gus'kova, A. K. (No affiliation given). *Probl Gematol Pereliv Krovi* 24(2): 58-59; 1979.

Current Soviet literature on the epidemiology and etiology of hemoblastoses is summarized briefly. The fact that certain ethnic factors, as well as sex and age, can affect the frequency of various variants of leukemia is indicative of their important role in leukemogenesis. (no refs)

- 79-1288 Multiple Myeloma: A Cluster in Virginia?** (Eng) Ende, M. (121 S. Market St., Petersburg, VA, 23803). *Va Med* 106(2): 115-116; 1979.

A community cluster of multiple myeloma was investigated. Between 1971 and 1978, 15 cases of multiple myeloma occurred in a small target area of Petersburg, Virginia. The 15 cases were among a total of 21 diagnosed in the entire city of Petersburg. The observed incidence of the disease in the target area far exceeded the expected rate of 1.6-2.4/100,000, the population of the target area being 15,000-17,000. Detailed histories revealed no association between the development of multiple myeloma and contact with Kepone, a chemical reported to have affected workers in a nearby community. The target area does contain a large number of industrial plants, with family residences in close proximity, and there are three that deal with lumber and millwork. Total protein examinations of 305 patients, 159 of whom came from the cluster area, revealed only one suspected case of multiple

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myeloma; however, this person may have monoclonal gammopathy from another cause. (10 refs)

- 79-1289 Diet, Hormones, and Breast Cancer.** (Eng) Kent, S. (Woodstock, NY). *Geriatrics* 34(1): 83-90; 1979.

A review of recent literature suggests that reducing dietary fats may protect against breast cancer by altering prolactin levels. However, attempts to duplicate in humans the anti-breast cancer effect of prolactin control in rats have failed. (38 refs)

- 79-1290 Epidemiology of Breast Carcinoma.** (Ger) Margreiter, R. (Chirurgische Universitätsklinik, Anichstrasse 35, A-6020 Innsbruck, Austria). *Wien Med Wochenschr* 128(24): 747-752; 1978.

Epidemiological studies of breast cancer are reviewed with special regard to risk factors. The incidence in men is <1% of that in women, and breast carcinoma is very rare in women aged <20 yr. Unlike the trend in Japan and other Asiatic countries, the incidence increases with advancing age. Generally, it is highest in women at high socioeconomic levels. The incidence is especially high among white women in western countries. No relationship was found between breastfeeding and breast cancer, but the incidence is high among nuns. The incidence increases with increasing age at menopause, which indicates the involvement of endogenous hormones and suggests an etiological role for exogenous hormones, such as oral contraceptives. Nutrition and other environmental factors also play a role, because women emigrating from countries with a low incidence to countries with a high incidence develop breast cancer more frequently than the women who did not emigrate. Breast carcinoma is related to the consumption of animal fats and to obesity. Mothers and sisters of breast carcinoma patients have a twofold greater risk than women without breast cancer in their family. Particles similar to murine mammary tumor virus were found in the milk of breast cancer patients and their female relatives. Breast cancer risk was found to be two to four times as high in Japanese atomic bomb survivors who were exposed to about 90 rads than in the general population. Fibrocystic mastopathy increases breast cancer risk by a factor of 4. (87 refs)

- 79-1291 Smoking and Lung Cancer: The Problem of Inferring Cause.** (Eng) Burch, P. R. (Dept. Medical Physics, Univ. Leeds, Leeds, England). *J R Stat Soc A* 141(part 4): 437-477; 1978.

Studies of the associations between smoking and lung cancer and their connection with sex and country are reviewed. The data in these studies corroborate the pure constitutional and combined theories but conflict with the pure causal theory of lung cancer and smoking. The sex and age distributions of deaths from lung cancer, as recorded by the Registrar Gen-

eral of England and Wales for 1901 to 1970, were analyzed by 5-yr intervals. Most of the recorded increase in lung cancer deaths was in the higher age groups (>45 yr old). Analysis of the temporal trends for lung cancer does not support the idea that the tumors were caused mainly by changes in smoking habits. The trends in lung cancer mortality among British male doctors, many of whom are exsmokers, also do not support the theory of a causal association between smoking and lung cancer. The age patterns of death rates (1960-1961) in 26 national populations with a wide range of death rates were all similar when analyzed mathematically. This series of coincidences is unlikely to be accidental, and it suggests that the kinetics of onset and death from lung cancer are fairly uniform throughout the world. From the evidence it is argued that no definitive conclusions can be reached about the extent of any causal link between smoking and lung cancer. Any appreciable causal action is unlikely to involve initiating or promoting mechanisms, but precipitation of forbidden clones in genetically predisposed hosts is consistent with the age patterns of lung cancer. (103 refs)

- 79-1292 Malignant Ovarian Tumors.** (Ita) Mossetti, C. (I. Clinica Ostetrica e Ginecologica, Università di Torino, Turin, Italy); Compagnoli, C.; Gilli, V. *Minerva Ginecol* 30(12): 1111-1122; 1978.

Epidemiological studies of malignant ovarian tumors (OT) are reviewed. Serous carcinomas account for about 46% of all OT, solid carcinomas for 24%, endometrioid carcinomas for 15%, and mucinous carcinomas for 13%. The incidence of malignant OT is lowest in Spain (2.6/100,000) and Japan (2.8/100,000) and highest in Sweden (15.1/100,000). The incidence is highest in the age bracket 50-65 yr. Previous dysmenorrhea and endometriosis are more frequent in patients with OT than in the general population. The incidence of OT is higher in nullipara and single women and in subjects with blood Group A, but there is no relationship between a family history of these tumors or the development of obesity and OT. A history of parotitis is more common in tumor-free women than in tumor patients. The incidence of OT is higher in developed countries and in the upper socioeconomic classes than in underdeveloped countries and in the lower classes. (39 refs)

- 79-1293 Cancer of the Urinary Bladder--Epidemiology and Aetiology.** (Eng) Morrison, R. (Radiotherapy Dept., Hammersmith Hosp., London, England). *Urol Res* 6(4): 183-184; 1978.

Geographical variations in bladder cancer incidence and known etiological factors are reviewed. Available data suggest that the incidence is highest in England and Wales. The incidence is also high in Egypt, where the disease is associated with bilharzia. Substances possibly associated with bladder cancer include chemicals used in aniline dye manufacturing, caffeine, aromatic amines, phenacetin, cyclophosphamide, and substances in cigarette smoke. (15 refs)

- 79-1294 Dietary Factors in the Aetiology of Gastrointestinal Cancer.** (Eng) Cummings, J. H. (MRC Dunn Clinical Nutrition Center, Addenbrooke's Hosp., Trumpington St., Cambridge, England). *J Hum Nutr* 32(16): 455-465; 1978.

Current epidemiological evidence that supports a role of dietary factors in the etiology of gastrointestinal (GI) cancer is reviewed. Of the total cancer deaths occurring annually in England and Wales, 32% (approx 40,000) are due to GI cancers, mainly in the esophagus, stomach, pancreas, and large bowel. Nutritional factors have been implicated in the cause of each of these cancers, and they probably act by promoting the effect of carcinogens consumed in diet or produced by the metabolic processes of the gut or its flora. Esophageal cancer shows the most striking geographic variation in incidence of all cancers, and etiological factors clearly vary in different parts of the world. Although no specific carcinogen has been identified, epidemiological evidence suggests that a variety of dietary factors, both nutritional deficiencies and excesses, may promote the tumor-inducing effect of carcinogens. A highly regarded hypothesis is that the ingestion or formation in the stomach of nitrosamines causes gastric carcinoma. Nitrosamine formation is enhanced by dietary nitrite and nitrate ingestion and inhibited by low temperatures (2 C) and vitamin C. The presence of bile acids is thought to enhance or promote the carcinogenicity of substances in the large intestine, and increased fecal bile acid excretion has been correlated with increased animal fat intake. High protein diets have been related to increased colon cancer incidence, possibly due to the presence of bacterial protein metabolites such as ammonia, phenol, p-cresol, and tryptophan metabolites, which may be tumor promoters. Dietary fiber may be a protective factor in large bowel cancer. The main risks of pancreatic cancer may be related to dietary fat intake and cigarette smoking and, possibly, protein intake. (62 refs)

- 79-1295 Diet and Colon Cancer.** (Eng) Graham, S. (Bldg. 2, Room 313, Spaulding Quadrangle, Univ. New York at Buffalo, Buffalo, NY, 14261); Mettlin, C. *Am J Epidemiol* 109(1): 1-20; 1979.

The effects of dietary fiber, animal fats, and vegetables on the risk of colon cancer are reviewed, as are problems associated with measuring dietary habits. One epidemiologic study suggests that a frequent intake of fibrous foods is associated with a low risk of colon cancer. A greater body of data suggests that a decreased risk of colon cancer is associated with eating vegetables and an increased risk is associated with a high meat or beef diet. Inconsistencies in findings and a relative paucity of data make definite conclusions imprudent, however, and suggest the need for further inquiry. Laboratory studies will be needed, as will studies on the past eating habits of humans. Despite its crudeness, the interview approach

shows some promise of aiding in the latter studies and of shedding light on the epidemiology of colon cancer. (48 refs)

- 79-1296 Dietary, Environmental, and Hereditary Factors in the Development of Colorectal Cancer.** (Eng) Lipkin, M. (Dept. Medicine, Cornell Univ. Medical Coll., New York, NY). *Cancer Bull* 30(6): 196-201; 1978.

Studies concerning factors involved in the etiology of colorectal cancer are reviewed. There is strong evidence to indicate that environment has a role in the development of colorectal cancer, but the most important elements involved are unclear because of conflicting findings. Some investigators believe that metabolic products of biliary metabolism, low dietary fiber content, and bacterial and intestinal cellular enzymes are key factors in increasing colon cancer risk. This relationship is supported by studies of many populations, but there are conflicting reports, particularly studies carried out in Finland and in groups such as the Mormons and Seventh-Day Adventists. The development of colorectal cancer has been shown to be influenced by genetic predisposition. Recent findings have indicated that familial associations of colon cancer in the general population are higher than those in control groups, suggesting that inherited factors may have a greater role in the genesis of colorectal cancer than has been generally believed. Specific abnormalities have been observed in the cells and intestinal contents of individuals with a hereditary predisposition to colorectal cancer. These abnormalities, which are tabulated here, are now serving as indices for studies of high-risk population groups and studies attempting to define interactions between cells genotypically predisposed to neoplasia and carcinogenic or promotor elements. (57 refs)

- 79-1297 Concepts in the Etiology and Prevention of Large Bowel Cancer. The Role of Intestinal Microflora.** (Eng) Mastromarino, A. J. (Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX). *Cancer Bull* 30(6): 202-205; 1978.

Literature concerning the relationship between intestinal flora and large bowel cancer is reviewed. Epidemiologic and laboratory investigations have indicated that intestinal flora are involved in large bowel carcinogenesis. However, it is unlikely that the bacteria produce a carcinogen, although they may produce N-nitroso compounds. In addition, the flora produce secondary acid sterols that have demonstrated promoting activity in animal models and are found in increased concentrations in the feces of high-risk populations. It may be feasible to modify the enzymic activities of the gut flora and thereby modify their carcinogenic or cocarcinogenic potential. (44 refs)

- 79-1298 Enteric Microenvironment and Its Effect upon the Morbid Anatomy of the Colon: A Study of Colon Cancer, Its Precursors, and Its Companions in Hawaii Japanese.** (Eng) Stemmermann, G. N. (No affiliation given); Hayashi, T.; Yatani, R. *Pathol Annu* 13(1): 1-18; 1978.

Studies of colon cancer and other diseases of the colon in native Japanese and Hawaii Japanese are reviewed. Hawaii Japanese have colorectal cancer rates that are more than three times those of indigenous Japanese; the increased incidence is almost entirely accounted for by colonic tumors. Autopsy studies in indigenous and Hawaii Japanese indicate that both adenomatous and hyperplastic polyps and diverticulosis are more prevalent in Hawaii Japanese. The hyperplastic polyp is a more sensitive indicator of Westernization and has a closer site association with colon cancer than the adenomatous polyp. The bowel transit times are similar in both Japanese populations, indicating that there is no association between bowel transit time and the benign or malignant colorectal lesions common in Western societies. There are differences in the fecal flora in Japan and the US, eg, high *Escherichia coli* and *Streptococcus faecalis* counts are more typical of Japanese stools. Chemical analyses of feces showed no significant differences in the amounts of degraded and primary bile acids in the two populations and no significant increase in the amount of any unidentified bile salt in the Hawaii samples. In the *Salmonella typhimurium* mutagenicity assay, fecal samples from Hawaii Japanese showed more mutagenic activity than those from indigenous Japanese. It is concluded that differences in fecal bacteriology and mutagen activity exist between genetically similar populations at high and low risk for hyperplastic and adenomatous polyps and for carcinoma of the bowel and that these differences probably result from differences in diet and life style. (31 refs)

- 79-1299 Diagnosis and Management of Early Carcinoma of the Endometrium.** (Eng) Walton, L. A. (Div. Gynecologic Oncology, Dept. Obstetrics and Gynecology, Univ. North Carolina Sch. Medicine, Chapel Hill, NC, 27514). *J Natl Med Assoc* 70(5): 309-312; 1978.

The diagnosis and management of early carcinoma of the endometrium are reviewed. The incidence of this disease is increasing, and factors affecting this increase include usage of estrogens and oral contraceptives, delayed menopause, increasing longevity of women, and increasing use of diagnostic methods. (17 refs)

- 79-1300 Adenocarcinoma of the Prostate in Perspective.** (Eng) Bruce, A. W. (Dept. Urology, Kingston General Hosp., Kingston, Ontario K7L 2V7, Canada); Mahan, D. E. *Can Med Assoc J* 119(9): 1077-1084; 1978.

Adenocarcinoma of the prostate is reviewed with respect to epidemiology, current staging systems, and treatment. The disease is particularly common among American Blacks (78.8/100,000) and rare in Mongoloid races (3.2-4.3/100,000). Incidence increases with age. Many patients with clinically defined disease remain asymptomatic, whereas in others there is rapid deterioration. The American Urological System is recommended for staging because of its ability to reflect changes in the biologic behavior of the neoplasm. Rectal examination of the prostate and adequate biopsy provide the most accurate information on extent of local spread and histopathology. Pedal lymphangiography has not proved accurate for assessing lymphatic spread in early carcinoma of the prostate. Pelvic lymphadenectomy is done in many centers prior to radical surgery or radiotherapy because it provides accurate information on the extent of lymph node involvement. Radionuclide bone scanning is far more sensitive for detecting bone metastases than roentgenographic techniques, but it is nonspecific and fails to detect very early microscopic bone involvement. Immunologic methods for the analysis of prostatic acid phosphatase have proved superior to enzymatic methods used previously. (88 refs)

- 79-1301 Occupational Cancer Risk (Letter to Editor).** (Eng) Rall, D. P. (Natl. Inst. Environmental Health Sciences, P.O. Box 1223, Research Triangle Park, NC, 27709). *Science* 203(4377): 224-226; 1979.

Responses to a previous letter containing various industry-generated criticisms of the Department of Health, Education, and Welfare draft report "Estimates of the fraction of cancer in the United States related to occupational factors" are presented. The purpose of this report was to demonstrate that a careful consideration of the multifactor etiology of most cancers would indicate that occupational exposures play a more significant role in the onset of this disease than has been generally recognized. (2 refs)

- 79-1302 Asbestos and Mesothelioma: A Review.** (Eng) Kannerstein, M. (No affiliation given); Churg, J.; McCaughey, W. T. *Pathol Annu* 13(1): 81-129; 1978.

The properties and biological effects of asbestos are reviewed with emphasis on its association with mesothelioma and on the diagnosis and pathology of the disease. Clinical and epidemiologic studies have associated all types of asbestos with asbestosis and carcinoma of the lung. Asbestos is the only substance that has been shown to have an epidemiologically meaningful association with mesothelioma. The incidence of mesothelioma has increased strikingly since the 1950's, with nearly all cases being in persons occupationally exposed to asbestos. In most cases the process is primarily

in one cavity, and a pleural origin is more common than a peritoneal one. Metastasis is frequent but it is not generally extensive. The microscopic features of mesothelioma range extensively from the pure epithelial to the mesenchymal form, with a spectrum of intermediate and combined forms. In diffuse malignant mesothelioma, there is a greater multiplicity of cell types and patterns at any stage of differentiation than in most neoplasms. A hyaluronic acid concentration of $> 120 \mu\text{g}$ in mesotheliomatous effusions is suggestive of mesothelioma; when coupled with suggestive cytology or histology, this finding may make the diagnosis more certain. The incidence of mesothelioma is expected to reach a peak in the 1980s. Although the existence of a cancer hazard associated with general asbestos air pollution has not been proved, it has not been excluded. (161 refs)

- 79-1303 Nature and Nurture in the Disease Patterns of Africa. The Twentieth Maude Abbott Lecture.** (Eng) Hutt, M. S. (No affiliation given). *Pathol Annu* 13(1): 19-27; 1978.

The epidemiology of three dissimilar diseases, Burkitt's lymphoma (BL), tropical splenomegaly syndrome (TSS), and endomyocardial fibrosis of Davies (EMF), in Uganda is reviewed. All three diseases are extremely rare in the mountainous areas of Southwest Uganda and in Rwanda and Burundi. In the Kampala area of Uganda, both TSS and EMF are much more common in immigrant Rwandans and related tribes than in the indigenous tribes. There is no differ-

ence in the frequency of BL in children in these two tribal groups, but most adults with BL are immigrants to Uganda. Mapping of the distribution of BL led to the suggestion that the tumor is related to *Plasmodium falciparum* malaria. In addition, patients with BL have a lower frequency of the sickle cell trait than controls. Thus, a genetic factor, by providing protection against malaria possibly by virtue of the high fetal Hb content in the RBC, appears to provide some protection against BL. Malaria may produce an immunologically susceptible host who reacts in an unusual way to some other causative agent. In the case of BL, the causative agent appears to be Epstein-Barr virus. The importance of genetic factors is, however, clearly shown by the protective effect of the sickle cell trait against malaria. (40 refs)

- 79-1304 The State of the Environment: Selected Topics 1977.** (Eng) Governing Council (United Nations Environment Program, Nairobi, Kenya). *Environ Int* 1(4): 205-218; 1978.

The ozone layer, environmental cancers, land loss and soil degradation, and firewood are discussed in this first annual report prepared by the Executive Director of the United Nations Environment Program. In an overview designed for the layman, most pertinent facets of the environmental cancer problem, including regional differences, occupational, drug, and chemical exposures, and prospects of cancer control are touched upon. (13 refs)

CHEMICAL CARCINOGENESIS

- 79-1305 Assay of 855 Test Chemicals in Ten Tester Strains Using a New Modification of the Ames Test for Bacterial Mutagens.** (Eng) McMahon, R. E. (Lilly Res. Labs., Indianapolis, IN, 46206); Cline, J. C.; Thompson, C. Z. *Cancer Res* 39(3): 682-693; 1979.

A method is described that allows assessment of the mutagenic potential of chemicals in eight histidine auxotrophs of *Salmonella typhimurium* and two tryptophan auxotrophs of *Escherichia coli* over a 10,000-fold concentration range with or without metabolic activation. This procedure was used to test 855 chemicals, 182 of which were found to be mutagenic for one or more of the tester strains. Among the mutagenic compounds were 20% of 299 chemicals used in chemical manufacturing or laboratory synthesis and 8% of 361 organic chemicals synthesized for evaluation as potential pharmaceutical or agricultural products. *S. typhimurium* strain TA100 was the most sensitive tester strain, but it was not useful for distinguishing between frameshift and base-substitution mutagens. Strains TA98 and TA1538 were efficient and reliable detectors of frameshift mutagens. Base-substitution mutagens were more reliably detected by *E. coli* strains WP2 and WP2 *uvrA* than by *S. typhimurium* strains G46 and TA1535. Testing mutagens by concentration gradient procedures can be used to indicate: the activity spectrum in tester strains; frameshift vs base-substitution mutagens; the minimal concentration at which auxotroph growth is inhibited; and the minimal concentration at which mutagenicity is observed. (15 refs)

- 79-1306 The *Salmonella* Mutagenicity Assay: Recommendations.** (Eng) de Serres, F. J. (Office Associate Director Genetics, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC); Shelby, M. D. *Science* 203(4380): 563-565; 1979.

Recommendations are put forth to provide guidelines for conducting the *Salmonella* mutagenicity assay, and they constitute minimum criteria by which reports of mutagenicity testing in the *Salmonella* plate assay can be evaluated. Strains TA1535, TA1537, TA1538, TA98, and TA100 should be used for routine testing. Overnight cultures of bacterial strains that have just reached a density of $1-2 \times 10^8$ viable cells/ml are most desirable for mutagen testing. Standard procedures for confirming the histidine requirement, deep-rough character, and UV sensitivity of tester strains are satisfactory, but tests for the presence of the R factor, which confers ampicillin resistance in strains TA100 and TA98, can be conducted more conveniently by using commercially available filter-paper disks containing 10 μ g ampicillin. Stock cultures should be checked periodically to ensure that close to 100% of the bacteria contain the R factor. The Aroclor 1254-induced rat liver S-9 preparation is the activation mix

of choice for routine screening. A minimum of two plates per dose level and an incubation period of 48-72 hr are recommended. Dose levels of 0.2 μ g-5 mg/plate should be tested. Preincubation is recommended in cases in which results from the standard plate assay are inconclusive. Negative and positive controls and controls for S-9 sterility should be run with each experiment. Test reports should include the means and indications of variability of the plate counts for the negative control, the positive controls, and each dose of the test compound. (2 refs)

- 79-1307 Isolation of Mutagens from Bacterial Nutrients Containing Beef Extracts.** (Eng) Vithayathil, A. J. (Center Biology Natural Systems, Washington Univ., St. Louis, MO, 63130); Commoner, B.; Nair, S.; Madyastha, P. *J Toxicol Environ Health* 4(1): 189-202; 1978.

Investigation was made of the slight augmentation of the mutation of *Salmonella typhimurium* strains TA1538 and TA98 in the presence of microsomes in the standard Ames mutagenicity test. The effect was considerably amplified in a modification of the Ames test using a liquid-culture system. By using this system and a series of extraction and thin-layer chromatography experiments, it was determined that the increased mutagenicity is caused by the presence, in the nutrient broth that is included in the bacterial inoculum added to the test plate, of substances that are converted by the microsomal enzyme system to actively mutagenic metabolites. Bacterial nutrients that include an extract prepared from beef muscle commonly contain on the order of 2.5 ppm of organic substances that are highly mutagenic in the *Salmonella* test system. These data suggest, therefore, that previously undetected presumptive carcinogens may be widely present in beef or in food preparations derived from it at a concentration sufficient to cause concern. (7 refs)

- 79-1308 Radiobiological Techniques Applied to Environmental Problems.** (Eng) Hahn, G. M. (Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305). *Radiat Res* 76(3): 459-470; 1978.

The application of specific cellular radiobiological techniques to toxicologic drug testing is illustrated by experiments utilizing Chinese hamster (HA 1) cells in culture under a variety of conditions. These techniques are useful not only in dose-response considerations of cell survival, but also in determining rate of mutagenicity and oncogenicity. Two specific techniques use the kinetics of recovery from potentially lethal damage as a possible, rapid means of assaying error-prone repair and Arrhenius theory as an aid in pinpointing specific mutagenic or carcinogenic reactions. Pitfalls involved when drug dose-effect relationships are determined in

tissue culture include the binding of drugs to growth surfaces, decay of drug activity, activity of agents released from inactivated cells, and the need for active intracellular metabolism for the correct estimation of some drug effects. Short- and long-term drug stability may be affected by pH or by the initial drug concentration. A drug may not exert its usual cytotoxic characteristics until after it is appropriately metabolically modified by the cell itself. If this metabolism is interfered with, the effectiveness of the drug may be reduced. It is hoped that careful observance of these subtle effects will avoid erroneous conclusions about important features of dose-response curves. (13 refs)

- 79-1309 Exploratory Techniques for the Determination of Potential Dose-Response Relationships Between Human Health and Air Pollution.** (Eng) Page, W. P. (Dept. Economics, West Virginia Univ., Morgantown, WV, 26506); Fellner, W. *J Environ Econ Manage* 5(4): 376-389; 1978.

The usefulness of selected multivariate statistical techniques, ie, factor analysis/correlation and canonical correlation techniques, for exploring new dose-response relationships between human health and air pollution was evaluated. Results obtained using these techniques were compared with those established in the literature through hypothesis testing procedures or laboratory work. This use of multivariate techniques is pretheoretical and should be interpreted as suggesting relationships that warrant further investigation with more traditional methodologies. Diseases for which data sets were examined included gastrointestinal, breast, respiratory system, urinary system, thyroid, and pleural cancer. Disease states were correlated with NO₂, SO₂, and SO₄ as pollutants. Using factor analysis/correlation techniques, highly significant results appeared between SO₂, SO₄, and gastrointestinal cancer and between NO₂ and breast cancer. Using canonical correlation techniques, positive correlations were obtained between SO₂ and SO₄ and gastrointestinal cancer and respiratory system cancer. The results conformed well to those of previously reported regression studies and lend credence to the use of these pretheoretical statistical methods. (18 refs)

- 79-1310 Determining the Distribution Pattern of Cadmium in the Human Liver.** (Ger) Kinkeldey, G. (Lehrstuhl Allgemeine und Kommunale Hygiene, Humboldt-Universität zu Berlin, Otto-Grotewohl-Strasse 1, DDR-108 Berlin, E. Germany). *Z Gesamte Hyg* 24(12): 927-929; 1978.

The hepatic cadmium distribution pattern was determined in samples taken from 13 sites in each of 10 livers taken from men aged 50-80 yr; the livers had no macroscopically visible pathological changes. The mean Cd concentration for each liver ranged from 1.22 to 1.59 µg/g. The variations were not statistically significant within one organ or from one organ to another. Sites of increased Cd concentration were found in all livers, but they varied from liver to liver; ie, there was

no preferred site for determining the Cd level in the liver. (5 refs)

- 79-1311 Structural and Histochemical Study of Ferridextran-induced LEW/CUB Tumours FLA, FLB, FLC, and FL.** (Eng) Elleder, M. (First Dept. Pathology, Faculty General Medicine, Charles Univ., Prague, Czechoslovakia); Jirasek, A.; Kren, V. *Folia Biol (Praha)* 24(6): 387-388; 1978.

The morphology and histochemical features of ferridextran-induced LEW/CUB tumors FLA, FLB, FLC, and FL were studied. During the latent period, the only recognizable histological structures were deposits of the iron pigment in the macrophages and extracellular spaces. The tumor was characterized as an anaplastic pleomorphic sarcoma, lacking any special histological pattern. The cytoplasm of the tumor cells was markedly oxyphilic and always recognizable. Individual tumor types could not be distinguished morphologically because the features were so variable. The following ultrastructural features were relatively frequent: (1) ribosomes, either free in the cytoplasm or bound in the rough endoplasmic reticulum; (2) lysosome-like dense bodies, often seen in the vicinity of the Golgi apparatus; and (3) coated vesicles situated beneath the cell membrane. True desmosomes were observed only occasionally and no production of collagen fibers was detected. Dehydrogenase activities were markedly decreased or absent in the necrotic areas. In tumor cells bordering this area, the activity of all dehydrogenases examined was moderately increased. No structural or histochemical features were found that helped to determine tumor histogenesis, and no clear-cut differences were observed that could be linked to the varying biological behavior of the different tumors. (1 ref)

- 79-1312 Lack of Cytogenetic Effects in Mice or Mutations in Salmonella Receiving Sodium Fluoride.** (Eng) Martin, G. R. (Lab. Developmental Biology and Anomalies, Natl. Inst. Dental Res., NIH, Bethesda, MD, 20014); Brown, K. S.; Matheson, D. W.; Lebowitz, H.; Singer, L.; Ophaug, R. *Mutat Res* 66(2): 159-167; 1979.

There was no evidence of an increased frequency of chromosomal aberrations in the bone marrow or testis cells of Swiss-Webster and BALB/c mice given either 50 ppm fluoride in the drinking water over several generations or 100 ppm for 6 wk, compared with untreated controls. Fluoride was not mutagenic in a *Salmonella typhimurium* mutagenesis assay over a range of 0.1-2,000 µg fluoride per plate. (22 refs)

- 79-1313 Quantitative Studies of In Vitro Morphological Transformation of Syrian Hamster Cells by Inorganic Metal Salts.** (Eng) DiPaolo, J. A. (Lab. Biology, NCI, Bethesda, MD, 20014); Casto, B. C. *Cancer Res* 39(3): 1008-1013; 1979.

Twelve metal compounds were tested for transforming ability by direct application to Syrian hamster embryo cells (HEC) that had been seeded for colony formation. Four of these compounds were also tested by a transplacental in vivo-in vitro approach. Petri dishes were seeded with 300 HEC from a secondary culture plus an irradiated feeder layer of 6×10^4 HEC. Chemicals (0, 2.5, 5, 10, or 20 $\mu\text{g}/\text{ml}$) were added 24 hr later. Dishes were fixed and stained 9 days after seeding. Morphological transformation was induced by inorganic salts of Ni (2 different Ni salts), Cd, Cr, Be, and As, but not Fe, Ti, Tu, Zn, Al, and NiS amorphous. No transformation was observed in untreated controls. Lethality, indicated by a reduction in cloning efficiency, occurred with both carcinogenic and noncarcinogenic metal salts. Transformation of HEC was also observed after transplacental exposure to inorganic salts of Ni, Be, Cr, and Cd (pregnant hamsters were injected with 2.5 or 5 mg/g ip on gestation day 11). The transformed colonies had a variety of morphologies that reflected the cell types present in early passages and that were identical to those observed after organic carcinogen exposure. There are animal data for the carcinogenicity of all the positive metals except As. Acceptable evidence for human carcinogenicity is available for all positive metals except Cd, although there is a possibility of a relationship between occupational exposure to Cd and prostatic cancer. Although Cd and Cr were the most potent transforming agents in terms of dose-response relationships, the comparative potency of the metals could not be determined, since it would depend on the ionization potential of the metal, the inorganic salt form, and the possible biointeractions of the various metals. (49 refs)

- 79-1314 Carcinogenicity of Antitumor *cis*-Platinum(II) Coordination Complexes in the Mouse and Rat.** (Eng) Leopold, W. R. (McArdle Lab. for Cancer Res., Univ. Wisconsin Center Health Sciences, Madison, WI, 53706); Miller, E. C.; Miller, J. A. *Cancer Res* 39(3): 913-918; 1979.

cis-Dichlorodiammineplatinum(II) [DDP: total of 54-108 micromoles (μmol)/kg given in 5-19 weekly ip injections], *cis*-dichlorobis(cyclopentylamine)platinum(II) (DCP: total of 108 or 433 $\mu\text{mol}/\text{kg}$ given in 10 weekly ip injections), *cis*-dichlorobis(pyrrolidine)platinum(II) (DPP: 2.5 mg/wk for 6 wk, sc), and ethyl carbamate (5,600 $\mu\text{mol}/\text{kg}$ given as a single ip injection) were tested for their carcinogenicity in female CD-1 and A/Jax mice and male Fischer rats and for their mutagenicity in *Salmonella typhimurium*. All mice given 103-108 $\mu\text{mol}/\text{kg}$ DDP developed lung adenomas within 8 mo, the efficiency of tumor induction being similar whether the DDP was injected in 0.85% NaCl soln or as a suspension in trioctanoin. Of the mice given 433 $\mu\text{mol}/\text{kg}$ DCP, 95% developed adenomas. Both DDP and DCP induced more adenomas per micromole of compound administered than did ethyl carbamate. DDP alone did not induce any gross skin tumors, but 50% of the mice treated topically with 0.6% croton oil while being given ip DDP developed papillomas at the site of application of the croton oil. Mice treated with croton oil alone also did not develop any skin tumors. Of the mice given 2 g/kg ethyl carbamate, 61% developed papil-

lomas within 30 wk. DPP and, to a lesser extent DCP, induced sarcomas at the site of injection in rats as well as some metastasizing sarcomas and an epidermoid carcinoma of Zymbal's gland. DDP, DCP, and DPP were mutagenic for *S. typhimurium*, with DDP being the most active. Treatment of patients with platinum antitumor complexes may impose a risk of secondary tumor induction in long-term survivors. (34 refs)

- 79-1315 Synthesis and Therapeutic Testing of Mono- and Dialkyl Esters of Pentetic (Diethylenetriaminepentaacetic) Acid for Decorporation of Polymeric Plutonium.** (Eng) Guilmette, R. A. (Inhalation Toxicology Res. Inst., Albuquerque, NM, 87115); Parks, J. E.; Lindenbaum, A. *J Pharm Sci* 68(2): 194-196; 1979.

A series of partially esterified derivatives of pentetic acid (diethylenetriaminepentaacetic acid) were prepared in an attempt to promote increased removal of insoluble colloidal forms of plutonium from the liver, compared with that removed by pentetic acid alone. The dimethyl, diethyl, dibutyl, dioctyl, and monoethyl esters of pentetic acid were injected iv into female B6CF₁/Anl mice as their calcium chelates in saline 5 days after iv injection of polymeric Pu (1.0 $\mu\text{Ci}/\text{kg}$). None of the esters were effective in removing Pu from the liver. All the esters removed approx 20% of the Pu in the skeleton. When the esters were given together with pentetic acid, only the dioctyl ester showed enhanced removal of Pu compared with pentetic acid alone. All of the esterified compounds were more acutely toxic than pentetic acid. The small increase in effectiveness and the increased acute toxicity indicate that these esters are not practical in Pu decorporation therapy. (20 refs)

- 79-1316 Induction of Duodenal Serotonin Production by Dietary Sodium Selenite and Aflatoxin B₁.** (Eng) Lator, J. H. (Dept. Biology, Virginia Commonwealth Univ., Richmond, VA, 23284); Kimbrough, T. D.; Llewellyn, G. C. *Food Cosmet Toxicol* 16(6): 611-613; 1978.

Male Mongolian gerbils were fed diets supplemented with 5 ppm sodium selenite (Na_2SeO_3), 12.8 ppm aflatoxin B₁ (AFB₁), or Na_2SeO_3 + AFB₁ for 12 wk. The animals were then killed and their duodenal serotonin levels were determined. All three dietary supplements induced significant serotonin increases. The duodenal serotonin level in controls was 6 $\mu\text{g}/\text{g}$, compared with 12 $\mu\text{g}/\text{g}$, 24 $\mu\text{g}/\text{g}$, and 72 $\mu\text{g}/\text{g}$ in the animals given Na_2SeO_3 , Na_2SeO_3 + AFB₁, and AFB₁, respectively. The increase in the Na_2SeO_3 group may have been due to the metabolism of additional tryptophan absorbed from the gastrointestinal tract or to the increased activity of an enzyme that accelerates the rate of serotonin biosynthesis. The increase in the AFB₁ group could be explained partially by normal metabolism of higher available levels of tryptophan or by decreased peristalsis resulting in feed remaining longer in the intestinal tract and leading to increased digestion and absorption. The intermediate result shown by the

group given the combined diet may represent a combination of the mechanisms involved in the other two test groups. It is concluded that AFB₁, Na₂SeO₃, interact with serotonin metabolism both separately and in combination. (21 refs)

- 79-1317 Mutagenic Activity of Selenium Compounds.** (Eng) Noda, M. (Dept. Microbiology, Keio Univ. Sch. Medicine, Tokyo, Japan); Takano, T.; Sakurai, H. *Mutat Res* 66(2): 175-179; 1979.

Selenate and selenite were found to be weakly mutagenic in two bacterial assay systems: Kada's *rec* assay and Ames's Salmonella assay. In the Ames test, base-pair substitution occurred with both selenate and selenite (0.05 and 0.2 revertant/nanomole, respectively). (13 refs)

- 79-1318 Exposure of DNA to Two Carcinogens, Dimethyl and Diethylsulfate (Meeting Abstract).** (Eng) Kubinski, H. (Univ. Wisconsin, Madison, WI, 53706); Fiant, M.; Konopa, G.; Kubinski, Z. O. *Fed Proc* 38(3, part 1): 502; 1979. (no refs)

- 79-1319 Phenotypic Expression Time of Mutagen-induced 6-Thioguanine Resistance in Chinese Hamster Ovary Cells (CHO/HGPRT System).** (Eng) O'Neill, J. P. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Hsie, A. W. *Mutat Res* 59(1): 109-118; 1979.

The phenotypic expression time of ethyl methanesulfonate (EMS)-induced 6-thioguanine resistance in Chinese hamster ovary cells [CHO/hypoxanthine-guanine phosphoribosyltransferase (HGPRT) system] was studied using trypsin, EDTA, or ethylene glycol bis(β -aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA) for cell removal. The effect of 30 μ M hypoxanthine in the medium was also determined. Hypoxanthine had little or no effect on transcription rates or on the intracellular stability of the HGPRT enzyme, and max stable mutation frequencies were observed at 7 days' expression time using trypsin, EDTA, or EGTA. The duration of expression time was affected by subculture interval, and CHO cells could be maintained for 3 days between subculture during phenotypic expression with no detrimental effects on mutant expression. Continual cell growth and division, uninterrupted by subculture, resulted in a shortening of the expression time, max expression being obtained after six to eight cell divisions. Mutation induction and fixation were apparently completed during the initial three to four cell divisions, and completion of phenotypic expression did not require continued cell division thereafter. The data suggest that in the CHO/HGPRT system, expression time is a constant that is independent of the mutagenic agent and dose. (16 refs)

- 79-1320 The Control of *Plasmopara viticola* with the 1:1 Complex of Zineb with 2-(2-Aminoethylamino)ethanol and the Potential Effect of the Use of This**

Complex on Ethylenethiourea Residues. (Eng) Clifford, D. P. (Dow Chemical Co. Ltd., Crossbank Road, King's Lynn, Norfolk, England); Bruyns-Haylett, J. P. *Pestic Sci* 9(5): 493-495; 1978.

A 1:1 complex of the metal dithiocarbamate (DTC) zineb with 2-(2-aminoethylamino)ethanol was more active than zineb in greenhouse and field trials against the grape downy mildew *Plasmopara viticola*. Potentiation of the activity of metal DTC's, which tend to decompose to the carcinogen ethylenethiourea, (ETU), may allow ETU levels to be reduced by permitting a reduction in the amount of DTC needed to control a fungal pathogen. (14 refs)

- 79-1321 Enhanced Metabolism and Mutagenesis of Nitrosopyrrolidine in Liver Fractions Isolated from Chronic Ethanol-consuming Hamsters.** (Eng) McCoy, G. D. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595); Chen, C. B.; Hecht, S. S.; McCoy, E. C. *Cancer Res* 39(3): 793-796; 1979.

The effect of chronic ethanol consumption (35% of the total caloric intake for 4 wk) on the ability of isolated liver fractions to metabolize the carcinogen N-nitrosopyrrolidine (NPY) was studied using male Syrian golden hamsters. Chronic ethanol consumption markedly increased the content of cytochrome P-450 and the activities of aniline hydroxylase and NPY α -hydroxylase in liver microsomes. NADPH-cytochrome c reductase was increased to a lesser extent, and the activities of glucose-6-phosphatase and benzo(a)pyrene hydroxylase were not affected. The postmitochondrial supernatants from ethanol-consuming animals were 4- to 5-fold more effective in converting NPY to a mutagen for *Salmonella typhimurium* than were those from control animals. It is concluded that α -hydroxylation is probably the mechanism whereby NPY is converted to a mutagen and that this pathway can be induced by ethanol. (38 refs)

- 79-1322 Factor VIII Content as Evidence for Endothelial Origin of Vinyl Chloride Associated Liver Angiosarcoma (Meeting Abstract).** (Eng) Fortwengler, H. P. (Univ. Louisville Sch. Medicine, Louisville, KY, 40232); Jones, D.; Tamburro, C. H.; Espinosa, E. *Fed Proc* 38(3, part 1): 999; 1979. (1 ref)

- 79-1323 The Clinical Features of Hepatic Angiosarcoma: A Report of Four Cases and a Review of the English Literature.** (Eng) Locker, G. Y. (Clinical Pharmacology Branch, NCI, Bldg. 10, Room 6N119, 9000 Rockville Pike, Bethesda, MD, 20014); Doroshow, J. H.; Zwelling, L. A.; Chabner, B. A. *Medicine (Baltimore)* 58(1): 48-64; 1979.

The clinical features and treatment of hepatic angiosarcoma are discussed based on four case reports and a review of 99 cases from the English literature. An apparent etiology was

identified in 43/103 cases: vinyl chloride in 22, thorotrast in 15, arsenicals in 2, radium in 1, and underlying hemochromatosis in 3. The tumor was most common in middle-aged men. The most common symptoms were abdominal pain, weakness, fatigue, and wt loss, and the most common presenting physical findings were hepatomegaly, ascites, and jaundice. Abnormalities in liver function tests, thrombocytopenia, and elevated prothrombin time were frequent laboratory findings. Arteriography was a valuable diagnostic tool, as was open biopsy at surgery. However, liver biopsy was accompanied by both morbidity and mortality, especially related to bleeding. Problems encountered during the clinical course included hepatic failure, intraabdominal and gastrointestinal bleeding, and peripheral destruction of blood elements. The median survival time from the first symptom was 5.5 mo, and only 3% of the patients lived > 2 yr. (144 refs)

79-1324 In Vivo Trapping of a Vinyl Chloride Metabolite by Means of 3,4-Dichlorobenzethiol.

(Eng) Muller, G. (Institut für Staublungenforschung, Westring 10, D-4400 Münster, W. Germany); Norpeth, K.; Owzarski, W. *Int Arch Occup Environ Health* 42(2): 137-139; 1978.

A method for trapping metabolites of vinyl chloride (VC) and 2,2'-dichlorodiethylether (DDE) is reported. Rats treated with VC and 3,4-dichlorobenzethiol excrete S-2(3,4-dichlorothiophenyl)acetic acid in the urine. The structure of the compound was confirmed by gas chromatography-mass spectrophotometry. Similar results were obtained with DDE. Thus, the formation of ultimate carcinogens from nonelectrophilic precursors can be proved by the use of nucleophilic trapping agents both in vitro and in vivo. (9 refs)

79-1325 Head-Space Gas-Chromatographic Analysis of Vinyl Chloride Monomer in Rat Blood and Tissues.

(Eng) Zuccato, E. (Istituto di Ricerche Farmacologiche "Mario Negri", Via Eritrea 62, 20157 Milan, Italy); Marcucci, F.; Fanelli, R.; Mussini, E. *Xenobiotica* 9(1): 27-31; 1979.

Vinyl chloride monomer (VCM) levels in rat blood and tissues were measured by a head-space gas chromatograph fitted with a flame ionization detector. Male CD rats were given VCM (1, 5, or 10 mg/kg iv or 10 mg/kg po) and killed 1-120 min later. VCM deposition was determined in blood, liver, kidney, brain, and lung. VCM was distributed rapidly after iv administration; blood had the highest concentration at 1 min, but brain and kidney levels attained equilibrium with blood levels within 2 min of injection. VCM in both blood and tissues was no longer detectable at 15 min for the highest iv dose and at 4 min for the lowest. VCM concentrations were lower in the lung than in blood and other organs at all times. Liver concentrations were generally lower than those of brain and kidney. VCM reached a high concentration in blood at 5 min after po administration, indicating rapid absorption from the gastrointestinal tract. At 60 min it was detectable

only in traces, and at 120 min it was no longer detectable. VCM concentrations in the liver were higher than those in blood up to 20 min, but they decreased faster than those in the other tissues, suggesting that metabolism by the liver may determine the disposition of VCM. The technique described is sensitive to 5 nanograms (ng)/ml VCM in blood and 30 ng/g in tissues. (15 refs)

79-1326 Carcinogenicity of Vinyl Chloride and Vinylidene Chloride.

(Eng) Lee, C. C. (Midwest Res. Inst., 425 Volker Blvd., Kansas City, MO, 64110); Bhandari, J. C.; Winston, J. M.; House, W. B.; Dixon, R. L.; Woods, J. S. *J Toxicol Environ Health* 4(1): 15-30; 1978.

The effects of exposure to 50, 250, or 1,000 ppm vinyl chloride (VC) or 55 ppm vinylidene chloride (VDC) for 6 hr/day, 5/days/wk, were studied in albino CD-1 mice and CD rats. The animals were killed after 1, 2, 3, 6, 9, or 12 mo. Bronchioloalveolar adenomas developed in 12/63, 22/63, and 48/69 mice exposed to 50, 250, and 1,000 ppm VC, respectively. Bronchioloalveolar adenomas developed in 6/35 animals exposed to VDC. Three of 29, 23/63, and 31/69 mice exposed to 50, 250, and 1,000 ppm VC, respectively, developed hemangiosarcomas (HS) in the liver. In the mice exposed to VDC, HS developed in the livers of two males and one female. Mammary gland tumors occurred in 9/34, 3/34, and 13/36 female mice exposed to 50, 250, and 1,000 ppm VC respectively, and they included ductular adenocarcinomas and squamous and anaplastic cell carcinomas with metastasis to the lung. Malignant lymphomas were found in various organs of mice exposed to VC but not in any of the mice exposed to VDC. Twelve of 70 and 21/70 rats exposed to 250 and 1,000 ppm VC, respectively, developed HS in the liver; 3/34 female rats exposed to 250 ppm VC and 13/70 rats exposed to 1,000 VC also developed HS in the lung. Two of 36 male rats exposed to VDC developed HS in the mesenteric lymph node or sc tissue. It is concluded that VC is highly carcinogenic in mice; the incidence and severity of the tumors increased with dose and length of exposure. Rats were more resistant to the carcinogenic effects of VC and VDC. (26 refs)

79-1327 Role of Liver Glutathione in 1,1-Dichloroethylene Metabolism and Hepatotoxicity in Intact Rats and Isolated Perfused Rat Liver.

(Eng) Reichert, D. (Institut für Pharmakologie, Universität Würzburg, Versbacher Strasse 9, D-8700 Würzburg, W. Germany); Werner, H. W.; Henschler, D. *Arch Toxicol (Berl)* 41(3): 169-178; 1978.

The role of liver glutathione in the metabolism and hepatotoxicity of 1,1-dichloroethylene (vinylidene chloride: VDC) was studied after po administration of 1,000 mg/kg VDC to female Wistar rats and after perfusion of isolated rat livers with 26.0 µg/ml VDC. After po administration, VDC lowered the liver glutathione concentration in a dose-dependent fashion. Glutathione levels dropped to approx 30% of control values after 4 hr; however, these levels returned to control

values within 24 hr. Addition of VDC to the perfusate caused a 23% drop in the glutathione concentration in isolated livers after 90 and 180 min of perfusion. The decrease was more pronounced when diethyl maleate, a mercapturic acid precursor, was also added to the perfusate. VDC metabolism was lowered by 18% after diethyl maleate-induced depletion of the reduced liver glutathione pool in livers from fed, but not fasted, rats. Increases in the extra-hepatic glutathione pool did not produce a change in total VDC conversion. A VDC-induced reduction in liver glutathione did not increase liver SGOT or SGPT levels in the perfused liver, but the lactate/pyruvate ratio was significantly increased. These findings indicate that there is no correlation between the liver glutathione level and the hepatotoxicity of VDC in fasted rats. (22 refs)

79-1328 Exchange of Comments: Analytical Methods of Bis(chloromethyl) Ether in Air (2 Letters to Editor). (Eng) Yao, C. C. (Poly-Tech Labs., Inc., P.O. Box 15623, Orlando, FL, 32858); Zollinger, H.; Kallos, G. J.; Solomon, R. A.; Tou, J. C. *Anal Chem* 51(2): 299-302; 1979.

The validity of the derivative method for determining levels of bis(chloromethyl) ether (BCME) in air, in which BCME is converted by trichlorophenol and methoxide in methanol into a derivative that is then assayed by gas chromatography, is questioned. In a reply, proponents of the method state that factual data supporting the criticism are not presented and that the derivative method, which is specifically designed to determine ppb levels of BCME in air, has been repeatedly shown to be chemically and technically sound. (30 refs)

79-1329 Cytogenetic Investigation of Occupational Exposure to Epichlorohydrin. (Eng) Picciano, D. (Office Carcinogen Identification and Classification, Occupational Safety and Health Admin., Dept. Labor, Washington, DC, 20210). *Mutat Res* 66(2): 169-173; 1979.

Cytogenetic studies were conducted on peripheral lymphocytes from 93 workers currently exposed to epichlorohydrin and from 75 persons seen for preemployment examination. A total of 200 cells/individual were scored for chromatid breaks, chromosome breaks, marker chromosomes, severely damaged cells, and total abnormal cells. Cells from the epichlorohydrin workers had a marked increase in all five categories of aberrations, compared with those from the nonexposed individuals. The difference was statistically significant in all categories except marker chromosomes. These results confirm those of a previous cytogenetic study of 35 epichlorohydrin-exposed workers. (9 refs)

79-1330 Lack of Effect of Trichloropropene Oxide on Benzo(a)pyrene Tumor-initiating Activity on Mouse Skin. (Eng) Alexandrov, K. (Institut de Recherches Scientifiques sur le Cancer, 94800-Villejuif, France); Dan-

sette, P. M.; Flodrops, M.; Frayssinet, C. *Eur J Cancer* 15(1): 77-83; 1979.

The effect of the epoxide hydratase inhibitor 1,1,1-trichloro-2,3-propene oxide (TCPO) on the induction of skin cancer by benzo(a)pyrene (BP) was studied in male Swiss mice. BP [0.1 micromole (μ mole)] with or without TCPO (2 μ mol) was applied either once (day 1) or twice (days 1 and 3) to the skin of the backs of mice shaved 24 hr earlier. Thereafter, the mice were given weekly applications of croton oil (20 μ l of 1% soln in acetone for 50 wk). Skin tumors started to appear 15 wk after initiation of the mice in the groups given BP with or without TCPO. The skin microsomal epoxide hydratase activity [48-52 picomoles of benzo(a)pyrene-4,5-diol/min/mg] was inhibited at 3 hr, but not at 16 or 24 hr, after application of BP with or without TCPO. TCPO had no in vitro effect on the 3 H-BP binding to epidermal DNA 24 hr after application of BP. Rapid trapping of TCPO by intracellular glutathione and/or nucleophiles would explain this lack of effect. These results are not in agreement with those of other studies, which showed an increase in the skin-tumor-initiating ability of BP following TCPO application. (31 refs)

79-1331 Mutagenicity Testing of Some Drug and Cosmetic Dye Lakes with the Salmonella/Mammalian Microsome Assay. (Eng) Brown, J. P. (Dynapol, 1454 Page Mill Road, Palo Alto, CA, 94304); Dietrich, P. S.; Bakner, C. M. *Mutat Res* 66(2): 181-185; 1979.

Ten commonly used coloring agents were tested in the *Salmonella typhimurium*/rat liver microsome mutagenicity assay. The colorants were mostly dye-alumina complexes or insoluble salts from which the dyes were solubilized prior to mutagenicity testing. Each agent was tested with all five basic tester strains (TA1535, TA100, TA1537, TA1538, and TA98), with and without microsomal activation. Three of the agents, D&C Red No. 19, D&C Red No. 36, and D&C Orange No. 17 were mutagenic. Thin-layer chromatographic analysis indicated that Orange No. 17 and Red No. 36 were pure. Red No. 19 (Rhodamine B) contained at least one impurity, which further testing indicated was probably the cause of its mutagenic activity. Each of the agents found to be mutagenic or to contain mutagenic impurities is currently used in drugs and cosmetics. (5 refs)

79-1332 Further Study of the Genetic Toxicity of Gentian Violet. (Eng) Au, W. (Dept. Biology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Butler, M. A.; Bloom, S. E.; Matney, T. S. *Mutat Res* 66(2): 103-112; 1979.

The mutagenicity of gentian violet (GV) was studied in the *Salmonella typhimurium* and *Escherichia coli* assays and in cytogenetic assays [Chinese hamster ovary (CHO) cells in vitro in the presence of rat liver microsomal (S9) fractions, chicken embryos, and mouse bone marrow cells in vivo]. GV

in the absence of S9 fraction, was bactericidal in the *Salmonella* assay at doses $\geq 10 \mu\text{g}$. It was not toxic in the presence of the S9 fraction. In the *E. coli* assay GV was mutagenic without activation, causing repairable DNA damage. Its activity was reduced, but not eliminated, by the S9 fraction. GV was not clastogenic in chick embryos or mouse bone marrow cells, and it failed to induce sister-chromatid exchanges. However, it was highly toxic to growing chick embryos at doses of 20, 100, 1,000, and 2,000 μg and depressed bone marrow mitotic activity after prolonged treatment. Chromosome damage induced in CHO cells by 5 $\mu\text{g}/\text{ml}$ GV was reduced to control levels by the S9 fraction. In cells treated with 10 $\mu\text{g}/\text{ml}$ GV, a proportional increase in the microsome fraction was required to reduce the induction of chromosome damage. At 20 $\mu\text{g}/\text{ml}$, chromosomes were severely damaged even in the presence of the S9 fraction. These results suggest that GV can be inactivated by the liver detoxification system. However, it is potentially hazardous to cells that are exposed to the dye directly. (15 refs)

79-1333 Human Metabolism of Caffeine (Meeting Abstract). (Eng) Callahan, M. M. (Arthur D. Little, Inc., Cambridge, MA, 02140); Robertson, R. S.; Lavin, M. J.; Yesair, D. W. *Fed Proc* 38(3, part 1): 584; 1979. (no refs)

79-1334 Comparative Effects of Sterculic and Malvalic Acids on the Hepatic Cytochrome P-450 System and Tumor Induction in Rainbow Trout (Meeting Abstract). (Eng) Bailey, M. L. (Dept. Food Science and Technology, Oregon State Univ., Corvallis, OR, 97331); Nixon, J. E.; Hendricks, J. D.; Pawlowski, N. E.; Loveland, P. M.; Sinnhuber, R. O. *Fed Proc* 38(3, part 1): 394; 1979. (1 ref)

79-1335 Long-Term Toxicity Study of Sorbitan Monostearate (Span 60) in Mice. (Eng) Hendy, R. J. (British Industrial Biological Res. Assoc., Woodmansterne Road, Carshalton, Surrey SM5 4DS, England); Butterworth, K. R.; Gaunt, I. F.; Kiss, I. S.; Grasso, P. *Food Cosmet Toxicol* 16(6): 527-534; 1978.

The effects of the food-grade emulsifier sorbitan monostearate (Span 60, 0%-4% of diet for 80 wk) on male and female TO mice were studied. Span 60 had no effects on condition or behavior. Males given 4% Span 60 had a higher total RBC count at 80 wk than untreated males, and total WBC counts were lower in females given 4% Span 60 than in untreated females. At autopsy, the body wts of males given 0.5% and 4% Span 60 were significantly lower than those of untreated males, and both males and females given 4% Span 60 showed enlargement of the kidneys and a higher incidence of nephrosis compared with controls. Other organ-wt changes appeared unlikely to be related directly to treatment. Most of the tumors observed during the study occurred with comparable frequency in the treated and control animals or more frequently in the controls. The no-untoward-effect level of

Span 60 in this study was 2.0% of the diet, or approx 2,600 mg/kg/day. (33 refs)

79-1336 Characterization of Microbial Metabolites of Lithocholic and Sulfolithocholic Acids by High Performance Liquid Chromatography (Meeting Abstract). (Eng) Kelsey, M. I. (NCI, Frederick Cancer Res. Center, Frederick, MD, 21501); Hwang, K. K.; Huang, S. S.; Pontzer, N. J.; Shaikh, B. *Fed Proc* 38(3, part 1): 510; 1979. (no refs)

79-1337 Octopine Catabolism by *Agrobacterium tumefaciens* (Meeting Abstract). (Eng) Unger, L. (Univ. Oklahoma Health Science Center, Oklahoma City, OK, 73190). *Fed Proc* 38(3, part 1): 395; 1979. (no refs)

79-1338 Toxicity of Patulin and Its Interaction with Penicillic Acid (Meeting Abstract). (Eng) Reddy, C. S. (Dept. Pharmacology & Toxicology, Univ. Mississippi Medical Center, Jackson, MS, 39216); Chan, P. K.; Hayes, A. W.; Williams, W. L.; Ciegler, A. *Fed Proc* 38(3, part 1): 679; 1979. (no refs)

79-1339 Mycotoxins in Foodstuffs. XII. The Influence of the Water Activity (a_w) of Cakes on the Growth of Moulds and the Formation of Mycotoxins. (Eng) Reiss, J. (Mikrobiologisches Laboratorium, Grahamhaus Stadt K.G., D-6550 Bad Kreuznach, W. Germany). *Z Lebensm Unters Forsch* 167(6): 419-422; 1978.

The influence of the water activity (WA: ie, the amount of free water directly available to microorganisms) of cakes (made of wheat flour, sugar, eggs, fat, and water) on the development and mycotoxin production of *Aspergillus flavus* (aflatoxins), *A. versicolor* (sterigmatocystin), *A. ochraceus* (ochratoxin A), *Penicillium chrysogenum* (citrinin), and *P. expansum* (patulin) was studied. All fungi showed max growth at the highest WA tested (0.92) and no ability to form visible colonies within 20 days at the lowest WA (0.82). In general, the highest yields of mycotoxins were formed at the highest WA values, although *P. chrysogenum* was unable to form citrinin at any WA. With the exception of sterigmatocystin, however, the yields of mycotoxins were not considerably influenced by the WA. In cakes with a WA of 0.92, the WA decreased after 10 days of incubation (water requirement during germination and initial growth) and then increased to values mostly above the initial levels after 20 days (initiation of secondary metabolism). (19 refs)

79-1340 Polarographic Study of Aflatoxins B₁, B₂, G₁, and G₂: Application of Differential-Pulse Polarography to the Determination of Aflatoxin B₁ in Various Foodstuffs. (Eng) Smyth, M. R. (Dept. Microbiology,

Colorado State Univ., Fort Collins, CO, 80523); Lawellin, D. W.; Osteryoung, J. G. *Analyst* 104(1234): 73-78; 1979.

Studies in which differential-pulse polarography was applied to the determination of aflatoxin B₁ in a variety of food products showed good agreement between the results of this method and those obtained by visual comparison of the fluorescence exhibited by the aflatoxin following thin-layer chromatographic separation. Electroactive interferences co-extracted from foods containing high amounts of lipids were removed by separation on a Sephadex LH-20 column. (9 refs)

79-1341 In Vivo Covalent Binding of Aflatoxin B₁(AFB₁) to DNA by Rats and Mice as a Function of Dose Size (Meeting Abstract). (Eng) Hayes, J. R. (Div. Nutritional Sciences, Cornell Univ., Ithaca, NY, 14853); Campbell, T. C. *Fed Proc* 38(3, part 1): 534; 1979. (no refs)

79-1342 Mutagenicity of Aflatoxin B₁, Activated by S-9 Fractions of Human, Rat, Mouse, Rabbit, and Monkey Liver, Towards *S. typhimurium* TA 98. (Eng) Norpoth, K. (Institut für Staublungenforschung und Arbeitsmedizin, Westfälischen Wilhelms-Universität Münster, D-4400 Münster, W. Germany); Grossmeier, R.; Bosenberg, H.; Themann, H.; Fleischer, M. *Int Arch Occup Environ Health* 42(3/4): 333-339; 1979.

The ability of human liver preparations to activate aflatoxin B₁ (AFB₁) to a mutagen was compared with that of liver preparations from male AF-Wistar rats, NMRI mice, male white New Zealand rabbits, and female Green monkeys using the *Salmonella*/microsome assay and *S. typhimurium* TA98 as the tester strain. Equal liver protein concentrations (1.2 mg/plate) were used to determine the number of his⁺ revertants induced per nanomole of AFB₁ (0.2-0.624 µg/plate). For the rat, rabbit, mouse, monkey, and human preparations, these values were 573, 480, 269, 233, and 36, respectively. With regard to the prediction of human susceptibility from this data, it is unlikely that a low capacity to activate AFB₁ by human liver measured in vitro could be reversed in vivo. It is emphasized, however, that it is impossible to predict in vivo susceptibility from in vitro mutagenicity results precisely. (37 refs)

79-1343 Effect of Phenobarbital and Diethyl Maleate Pretreatment on Covalent Binding of ³H-AFB₁ to Hepatic Macromolecules (Meeting Abstract). (Eng) Allen-Hoffmann, B. L. (Div. Nutritional Sciences, Cornell Univ., Ithaca, NY, 14853); Campbell, T. C. *Fed Proc* 38(3, part 1): 865; 1979. (no refs)

79-1344 Old and Young WI-38 Human Fibroblasts Differ in Their Susceptibility to Aflatoxin B₁ (Meeting Abstract). (Eng) Mathur, C. F. (York Coll. of Pennsylvania, York, PA, 17405); Ambler, E. T. *Fed Proc* 38(3, part 1): 823; 1979. (no refs)

79-1345 Metabolism of Aflatoxin B₁ and Identification of the Major Aflatoxin B₁-DNA Adducts Formed in Cultured Human Bronchus and Colon. (Eng) Autrup, H. (Human Tissue Studies Section, Lab. Experimental Pathology, NCI, Bethesda, MD, 20014); Essigmann, J. M.; Croy, R. G.; Trump, B. F.; Wogan, G. N.; Harris, C. C. *Cancer Res* 39(3): 694-698; 1979.

Studies showing that aflatoxin B₁ (AFB₁) can be activated by cultured human tissues and that the major adduct formed between DNA and AFB₁ is chromatographically identical to the adduct formed in rat liver (an organ susceptible to AFB₁ carcinogenesis) are reported. AFB₁ and benzo(a)pyrene (BP) were activated by both cultured human bronchus and human colon, as measured by binding to cellular DNA and protein. The binding of AFB₁ to DNA was dose-dependent, and the level of binding was higher in cultured human bronchus than it was in the colon. When compared to AFB₁, the binding level of BP to both bronchial and colonic DNA was generally higher. The major adducts formed in both tissues by the interaction of AFB₁ and DNA were chromatographically identical to 2,3-dihydro-2-(N⁷-guanyl)-3-hydroxyaflatoxin B₁ (structure I), with the guanyl group and hydroxy group in the trans-position, and an adduct that has been tentatively identified by other investigators as 2,3-dihydro-2-(N³-formyl-2',5',6'-triamino-4'-oxo-N⁵-pyrimidyl)-3-hydroxyaflatoxin B₁ (Structure II). Seventy percent of the radioactivity associated with bronchial DNA was found in these two peaks, and the ratio of radioactivity between the peaks was nearly 1. In colonic DNA, the ratio between structures I and II was approx 2. These observations add AFB₁ to the list of chemical procarcinogens metabolized by cultured human tissues, in which the carcinogen-DNA adducts are similar to the adducts formed in animal tissue susceptible to the carcinogenicity of AFB₁. (45 refs)

79-1346 Transplacental Action of Sodium Nitrite on Embryonic Cells of Syrian Golden Hamster. (Eng) Inui, N. (Section Cell Biology and Cytogenetics, Biological Res. Center, Japan Tobacco and Salt Public Corporation, Hatano, Kanagawa 257, Japan); Nishi, Y.; Taketomi, M.; Mori, M. *Mutat Res* 66(2): 149-158; 1979.

In utero NaNO₂ treatment (125, 250, or 500 mg/kg to pregnant hamsters by stomach tube on gestation day 11 or 12) produced a marked dose-dependent induction of 8-azaguanine- and ouabain-resistant mutations in Syrian golden hamster embryo cells. Cultured embryonic fibroblasts in the resting state also showed a marked dose-dependent increase in micronucleus formation but no increase in chromosome aberrations. The treatment also produced morphological and neoplastic transformation of the cells. (25 refs)

79-1347 Mutagenicity of Alkaloids in the *Salmonella*/Microsome System. (Eng) Wehner, F. C. (Natl. Res. Inst. Nutritional Diseases, South African Medical Res.

Council, 7505 Tygerberg, South Africa); Thiel, P. G.; Van Rensburg, S. J. *Mutat Res* 66(2): 187-190; 1979.

Evidence that some alkaloids are mutagenic in the *Salmonella*/mammalian microsome test is presented. In the presence of a liver microsome fraction, cycasin was mutagenic for strain TA1535, harmine HCl for TA1537, and retrorsine for TA1535 and TA1537; optimal concentrations were 2.5, 500, and 0.25 $\mu\text{g}/\text{plate}$, respectively. The other alkaloids tested (harmaline, harmame, and macrozamin) were not mutagenic. A base-pair-substituting mutagenic action by cycasin and a frameshift mechanism by harmine are indicated; retrorsine apparently possesses both. *Salmonella* strains containing R-factor plasmids were not reverted by the alkaloids. (15 refs)

- 79-1348 The Multiple Forms and Kinetic Properties of the N-Acetyl- β -D-hexosaminidases from Colonic Tumours and Mucosa of Rats Treated with 1,2-Dimethylhydrazine.** (Eng) Mian, N. (Dept. Experimental Pathology, Univ. Leeds, Leeds LS2 9LS, England); Herries, D. G.; Cowen, D. M.; Batte, E. A. *Biochem J* 177(1): 319-330; 1979.

N-Acetyl- β -D-hexosaminidase (AHA) activities in the colonic tumors and colonic mucosa of 1,2-dimethylhydrazine-treated male Wistar rats were compared. Mucosa contained two forms of AHA, A and B, as well as a third intermediate form. The tumors contained only A and B activities. Each form possessed both N-acetylglucosaminidase and N-acetylgalactosaminidase activities, and these activities could not be separated by a variety of techniques. The mucosa and tumor forms did not differ in terms of inactivation by AgNO_3 or HgCl_2 , inactivation by thimerosal, or response to neuraminidase. However, the K_m of the tumor form B enzyme was significantly lower than that for the mucosa form B. In addition, the tumor form B was significantly more strongly inhibited by monosaccharides, it was slightly more resistant to inactivation by p-hydroxymercuribenzoate, it was protected from inactivation by lower concentrations of glutathione of L-cysteine, and it was more resistant to thermal inactivation than the mucosa form B. The different forms of the AHA's were not interconvertible. The data support the belief that each enzyme form contains glucosaminidase and galactosaminidase activities at separate active sites. (43 refs)

- 79-1349 N,N-Dimethylformamide-induced Alteration of Cell Culture Characteristics and Loss of Tumorigenicity in Cultured Human Colon Carcinoma Cells.** (Eng) Dexter, D. L. (Dept. Medicine, Roger Williams General Hosp., 825 Chalkstone Ave., Providence, RI, 02908); Barbosa, J. A.; Calabresi, P. *Cancer Res* 39(3): 1020-1025; 1979.

A study was made of the effects of the polar solvent N,N-dimethylformamide (DMF: 0.8%) on cultures of human carcinoma cell lines DLD-1 and HCT-15 plus two sublines isolated from DLD-1 cells (clones A and D), and the results were compared with observations of untreated cells. There was a 4- to 5-day lag time before morphological

changes in treated cultures were induced completely. Colonies of all four cell types became less circular and more leaf-like at the edges and the cells became less refractile under the light microscope. Doubling times were increased significantly (by a factor of 2-3), saturation densities were reduced, and the ability to grow in soft agar was lost completely (vs a clonogenicity of up to 77% for untreated cells). Growth in the presence of DMF also markedly reduced the tumorigenicity of the cells. Ten of 10 nude mice that received an sc inoculum of 1×10^6 untreated cells developed tumors histologically similar to colonic adenocarcinomas in 10-14 days, but 9/10 nude mice inoculated with 1×10^6 treated cells have shown no sign of tumor 3-6 mo postinjection. Removal of DMF from the culture medium was accompanied within 4-7 days by the reappearance of tumorigenicity and the original cell culture characteristics. Apparently, DMF can reversibly effect the reversion of cultured human colon carcinoma cells to less malignant cell types. (31 refs)

- 79-1350 para-Nitrophenol Uridine Diphosphate Glucuronic Acid Transferase in Microsomes from Livers of Rats Fed Hepatocarcinogens (Meeting Abstract).** (Eng) Walston, K. K. (Oklahoma Medical Res. Foundation, Ardmore and Oklahoma City, OK, 73116); Kizer, D. E.; Griffin, M. J. *Fed Proc* 38(3, part 1): 654; 1979. (no refs)

- 79-1351 Phenoxyacids as Inhibitors of Testicular DNA Synthesis in Male Mice.** (Eng) Seiler, J. P. (Swiss Federal Res. Station, CH-8820 Wädenswil, Switzerland). *Bull Environ Contam Toxicol* 21(1/2): 89-92; 1979.

The abilities of five phenoxyacids to inhibit testicular DNA synthesis in male mice were studied. 2,4-Dichlorophenoxyacetic acid (2,4-D: 200 mg/kg, po), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T: 200 mg/kg, po), 2,4,5-T ester (200 or 400 mg/kg, po), 2-methyl-4-chlorophenoxyacetic acid (MCPA: 200 mg/kg, po), and 2-methyl-4-chlorophenoxypropionic acid (200 mg/kg, po) significantly depressed the uptake of labeled thymidine by testicular DNA. 2,4-Dichlorophenoxypropionic acid (200 mg/kg, po) did not significantly alter thymidine uptake, nor did 2,4,5-T ester at 50 or 100 mg/kg. The mutagenic activity of three of the compounds was previously reported to decrease in the order $\text{MCPA} > 2,4,5\text{-T} > 2,4\text{-D}$; their ability to inhibit testicular thymidine uptake decreased in the same order. (15 refs)

- 79-1352 Activation of 2-Acetylaminofluorene in the Nuclei of Rat Liver.** (Eng) Kawajiri, K. (Biochemistry Div., Saitama Cancer Center Res. Inst., Ina-machi, Kitaadachi-gun, Saitama-ken 362, Japan); Yonekawa, H.; Hara, E.; Tagashira, Y. *Cancer Res* 39(3): 1089-1093; 1979.

The role of the nuclear monooxygenase (NMO) system in the activation of 2-acetylaminofluorene (AAF), a potent hepatocarcinogen, in the nuclei of rat liver cells was investigated using an antibody against microsomal NADPH-cytochrome

c reductase. The relationship between microsomes (MS) and nuclei in the binding of AAF to DNA was also investigated. AAF bound to DNA when incubated with nuclei isolated from Sprague-Dawley rat livers. No binding occurred in the absence of NADPH, which suggests that binding was dependent on NMO. Binding was increased 17-fold by pretreatment of rats with 3-methylcholanthrene (3-MC: 10 mg/kg ip 24 hr before experiments) and inhibited by preincubation of nuclei with the antibody. Binding of AAF to DNA in untreated nuclei was increased by the addition of a small amount of MS (up to a nuclei: MS protein ratio of 0.3), but it gradually decreased upon the addition of higher amounts of MS. The increase in binding was fivefold greater in the presence of 3-MC-treated MS than in the presence of untreated MS. It was inhibited by preincubation of the MS with the antibody, indicating that AAF is activated by a microsomal monooxygenase system and that metabolically activated AAF reaches the nuclei from the endoplasmic reticulum. Addition of MS to 3-MC-treated nuclei decreased the binding of AAF to DNA. Addition of MS from untreated rats resulted in a greater decrease than MS from 3-MC-treated rats. These phenomena can be explained by changes in the influx and efflux of AAF activated in the nuclei and MS across the nuclear membrane. It is suggested that intracellular activation of AAF occurs not only in the endoplasmic reticulum but also in the nuclear envelope. (29 refs)

79-1353 Responsiveness of the Adrenergic Receptor in Parenchymal Cells Isolated from Livers of Rats Fed 2-Acetylaminofluorene (AAF) (Meeting Abstract). (Eng) Hornbrook, K. R. (Univ. Oklahoma Coll. Medicine, Oklahoma City, OK, 73190). *Fed Proc* 38(3, part 1): 540; 1979. (1 ref)

79-1354 The Effect of Time on the Incidence of Carcinomas Obtained by the Implantation of Paraffin Wax Pellets into Mouse Bladder. (Eng) Jull, J. W. (Cancer Res. Centre, Univ. British Columbia, Vancouver, British Columbia, Canada). *Cancer Lett* 6(1): 21-25; 1979.

The effects of paraffin wax pellets with and without added chemicals on the bladder epithelium of 3-mo-old B6AF1/J-type female F1 hybrid mice were studied over a 2-yr period. The pellets were implanted surgically into the mouse bladder lumen. The animals were killed after 40-50, 70-80, and 100-110 wk and examined for proliferative changes in the bladder. In the mice implanted with Leeds paraffin wax pellets, 7/66, 15/56, and 21/39 developed carcinomas at 40-50, 70-80, and 100-110 wk, respectively. In the mice implanted with Vancouver paraffin wax pellets, 0/36 and 9/27 developed carcinomas at 40-50 and 70-80 wk, respectively. In animals implanted with 1-phenylazo-2-naphthol-containing pellets, 20/60, 22/36, and 23/26 developed carcinomas at 40-50, 70-80, and 100-110 wk, respectively. Each of these tumor incidences was statistically significant compared with those in mice in which paraffin pellets alone had been implanted for equivalent periods. Pellets containing

N-2-fluorenylacetamide or its metabolites (1-hydroxy-N-2-fluorenylacetamide, 3-hydroxy-N-2-fluorenylacetamide, or N-2-fluorenylacetohydroxamic acid) gave very similar incidences of carcinomas whether or not they were carcinogenic by po or parenteral administration. These results indicate that the incidence of carcinomas increases with time, and they raise questions about the relative importance of the pellet and the chemical within it in the induction of bladder tumors. (9 refs)

79-1355 DNA-Protein Cross-linking by Chemical Carcinogens in Mammalian Cells. (Eng) Fornace, A. J. (Dept. Pathology, Peter Bent Brigham Hosp., Boston, MA); Little, J. B. *Cancer Res* 39(3): 704-710; 1979.

The induction of DNA cross-linking in human CRL 1220 and mouse C3H/10T1/2 fibroblasts by various carcinogens was investigated by alkaline elution. A dose-dependent increase in DNA cross-linking was seen following exposure of human fibroblasts to N-acetoxy-2-acetylaminofluorene (AAAF) and following exposure of mouse embryo cells to 7,12-dimethylbenz(a)anthracene. No cross-link effect was seen following treatment with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), benz(a)anthracene, benz(a)anthracene-5,6-dihydroepoxide, or metabolic inhibitors (sodium arsenite, potassium cyanide, and cycloheximide). The cross-linking appeared to be DNA-protein in nature, since proteinase treatment removed the effect. DNA single-strand breaks were also induced by several of these agents. In the case of AAAF and MNNG, approx 70%-90% of these breaks were rejoined after an 18-hr incubation in fresh medium, whereas repair of the cross-links induced by AAAF was slight at this time. (34 refs)

79-1356 Another Approach to In Vivo Estimation of Genetic Damage in Humans. (Eng) Pero, R. W. (Wallenberg Lab., Nucleic Acid Biochemistry, Univ. Lund, Fack 7031, S-220 07 Lund 7, Sweden); Mitelman, F. *Proc Natl Acad Sci USA* 76(1): 462-463; 1979.

Lymphocytes from 28 apparently healthy persons (25 men and 3 women, aged 22-66 yr) were analyzed simultaneously for (1) the level of in vivo chromosome aberrations after 72 hr of phytohemagglutinin stimulation, and (2) the induction of unscheduled DNA synthesis (UDS) after a 1-hr exposure to 10 μ M N-acetoxy-2-acetylaminofluorene (NA-AAF). A highly significant positive linear correlation existed between the two variables; the interindividual variations in NA-AAF-induced UDS paralleled the actual in vivo levels of chromosome damage. It is suggested that measurement of NA-AAF-induced UDS may be a rapid useful supplement in human genetic risk assessment. (18 refs)

79-1357 Carcinogenic Effect of N-Bis(2-hydroxypropyl)nitrosamine by a Single Administration in Rats. (Eng) Konishi, Y. (Dept. Oncological Pathology, Can-

cer Center, Nara Medical Univ., 840 Shijo-cho, Kashihara, Nara 634, Japan); Ikeda, T.; Yoshimura, H.; Kawabata, A.; Mikami, R. *Cancer Lett* 6(2): 115-119; 1979.

The carcinogenic effect of a single ip injection of 3 or 4 g/kg of N-bis(2-hydroxypropyl)nitrosamine (BHP) was studied in 7-wk-old male Wistar rats. Lung tumors (adenomas and adenocarcinomas) were seen in 100% of the rats in both treatment groups. Neoplasms were also induced in the thyroid (adenomas and adenocarcinomas) of 4/11 and 4/12 rats receiving 3 and 4 g/kg BHP, respectively, in the kidney of 1/12 rats receiving 4 g/kg BHP, and in the sigmoid colon of 1/11 rats receiving 3 g/kg BHP. No tumors were detected in control rats after 52 wk and no pancreatic neoplasms were detected. In contrast to the high incidence of bronchogenic adenomas and adenocarcinomas produced in this study, squamous cell carcinomas and adenosquamous cell carcinomas were the major lung tumor types that developed after po BHP administration. Thus, a relationship appears to exist between the route of BHP administration and the morphology of the induced lung neoplasms. (10 refs)

79-1358 Induction of Rat Lung Carcinoma by a Single Injection of N-Bis(2-hydroxypropyl)nitrosamine. (Eng) Konishi, Y. (Dept. Oncological Pathology, Nara Medical Univ., 840 Shijo-cho, Kashihara, Nara-ken 634, Japan); Ikeda, T.; Kawabata, A.; Yoshimura, H.; Mikami, R. *Gann* 69(6): 855-856; 1978.

The carcinogenicity of N-bis(2-hydroxypropyl)nitrosamine (DHPN, 3 or 4 g/kg given as a single ip injection) in 7-wk-old male Wistar rats was determined. All 23 rats sacrificed 52 wk after treatment had developed lung adenomas, and lung adenocarcinomas were found in 9/11 rats in Group 2 (3 g/kg) and 9/12 rats in Group 3 (4 g/kg). Group 1 was untreated (controls). Adenomas of the thyroid were detected in 2/11 Group 2 rats and in 3/12 Group 3 rats; thyroid adenocarcinomas were detected in 2 Group 2 rats and 1 Group 3 rat; an adenocarcinoma of the sigmoid colon was found in 1 Group 2 rat; and a renal cell carcinoma was found in 1 Group 3 rat. No tumors were found in Group 1 rats. The data demonstrate the carcinogenicity of ip DHPN and indicate that the DHPN-induced rat lung carcinoma is a useful model for studying the initiation and promotion of carcinogenesis. (9 refs)

79-1359 Mutagenicity of Some N- and O-Acyl Derivatives of N-Hydroxy-2-aminofluorene in V79 Chinese Hamster Cells. (Eng) Kuroki, T. (Dept. Cancer Cell Res., Inst. Medical Science, Univ. Tokyo, Shirokanedai, Minato-ku, Tokyo 108, Japan); Bartsch, H. *Cancer Lett* 6(2): 67-72; 1979.

The mutagenicity of four N- and O-acyl derivatives of N-hydroxy-2-aminofluorene (acyl: acetyl or myristoyl residue) was examined in V79 Chinese hamster cells in the absence of a metabolic activation system.

N-Myristoyloxy-N-acetyl-2-aminofluorene (5-50 μ M) was toxic and weakly mutagenic, inducing 8-azaguanine-resistant mutants in the cells in a concentration-dependent fashion. N-Acetoxy-N-myristoyl-2-aminofluorene (5-50 μ M) and N-myristoyloxy-N-myristoyl-2-aminofluorene (6.3-25.0 μ M) were neither cytotoxic nor mutagenic. Under the same conditions, N-acetoxy-N-acetyl-2-aminofluorene (4-16 μ M) was highly toxic and mutagenic. Neither of the two N-myristoyloxy derivatives was mutagenic in *Salmonella typhimurium*. These esters have been reported to produce local tumors at the site of their injection in rats, to be electrophilic toward methionine, and to induce unscheduled DNA synthesis in cultured human fibroblasts. However, the fact that some of the esters were not mutagenic in *S. typhimurium* or in V79 Chinese hamster cells emphasizes the need for multiple short-term tests in predicting the potential carcinogenic activity of chemicals. (10 refs)

79-1360 Validation and Characterization of the L5178Y/TK+/- Mouse Lymphoma Mutagen Assay System. (Eng) Clive, D. (Genetic Toxicology Lab., Burroughs Wellcome Co., Research Triangle Park, NC, 27709); Johnson, K. O.; Spector, J. F.; Batson, A. G.; Brown, M. M. *Mutat Res* 59(1): 61-108; 1979.

A specific-locus mutagenicity assay using L5178Y mouse lymphoma cells rendered heterozygous at the normally diploid thymidine kinase (TK) locus and supplemented with an exogenous in vitro metabolic activation system was validated. Validation took the form of dose-response data for 43 chemicals, including mutagens and carcinogens of varying potencies and several agents designed for human exposure. Mutagenicity and cytotoxicity in the presence or absence of noninduced and/or Aroclor-induced rat liver S-9 mix were compared for most of the chemicals. Twenty-five chemicals for which usable carcinogenicity data exist were used to construct an approx linear relationship between oncogenic potency in vivo and mutagenic potency in this system in vitro; linearity between these two endpoints extended over a > 100,000-fold range in potencies. Natulan, sodium saccharin, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene dimethylnitrosamine, diethylnitrosamine, and diethylstilbestrol, which are either negative or difficult to detect in the standard Ames assay, were mutagenic in this mammalian cell system. Characterization of the TK-/- mutants suggested that two mutagenic mechanisms contribute to their final yield. Large colony TK-/- mutants probably represent point or gene mutations affecting the TK locus. In addition, a class of small colony TK-/- mutants was described and characterized as being heritably growth-deficient; this and other properties suggest that these small colony TK-/- mutants originate by a heritable and viable chromosomal aberration. Most carcinogens and mutagens tested produced both classes of TK-/- mutants in this system; the relative proportions of small and large colony mutants were both mutagen- and dose-dependent. Comparative studies at the rapidly expressing TK locus and the slowly expressing hypoxanthine-guanine phosphoribosyltransferase (HGPRT) locus in these cells showed

that several carcinogens detected at the TK locus are non- or very weakly mutagenic at the HGPRT locus. This is consistent with the induction of slow-growing specific locus mutants by a chromosomal mechanism and their subsequent dilution during this long expression time. (47 refs)

79-1361 The Kinetics of Dimethylamino Radical Reactions in Simulated Atmospheres: The Formation of Dimethylnitrosamine and Dimethylnitramine (Meeting Abstract). (Eng) Lindley, C. R. (Ohio State Univ., Columbus, OH, 43210). *Diss Abstr Int B* 39(8): 3857; 1979. (no refs)

79-1362 Effects of Thiamine Deficiency on the Metabolism and Toxicity of Dimethylnitrosamine (Meeting Abstract). (Eng) Ruchirawat, M. (Mahidol Univ., Bangkok, Thailand); Mahathanatrakul, W.; Sinrathanant, Y.; Kittikool, D. *Fed Proc* 38(3, part 1): 869; 1979. (no refs)

79-1363 Oxidative Metabolism of Dimethylnitrosamine: Correlation with Toxicity. (Eng) Ruchirawat, M. (Dept. Pharmacology, Faculty Science, Mahidol Univ., Rama VI Road, Bangkok 4, Thailand); Shank, R. C. *J Toxicol Environ Health* 4(1): 161-172; 1978.

A study of the relationship between oxidative metabolism and acute dimethylnitrosamine (DMN) toxicity demonstrated that max DMN metabolism in the neonatal rat liver occurs between days 5 and 21 of age and in the kidney between days 15 and 21. Evidence suggesting that more than one enzyme may be responsible for DMN oxidation to CO₂ is presented. Rats were most sensitive to DMN toxicity at 5 days of age, but DMN conversion to CO₂ was not well-correlated with toxicity. (23 refs)

79-1364 Mechanism of Metabolic Activation of Dimethylnitrosamine (DMN) (Meeting Abstract). (Eng) Woo, Y. T. (USPHS Res. Lab., Tulane Medical Center, New Orleans, LA, 70118); Lai, D. Y.; Argus, M. F.; Arcos, J. C. *Fed Proc* 38(3, part 1): 536; 1979. (no refs)

79-1365 A Synergistic Effect of Nitrosodimethylamine on Sterigmatocystin Carcinogenesis in Rats. (Eng) Terao, K. (Res. Inst. Chemobiodynamics, Chiba Univ., 280 Chiba, Inohana 1-8-1, Japan); Aikawa, T.; Kera, K. *Food Cosmet Toxicol* 16(6): 591-596; 1978.

Male Wistar rats (4 wk old) were fed diets containing 10 ppm sterigmatocystin (STG), 10 ppm STG + 1 ppm nitrosodimethylamine (NDMA), 1 ppm STG + 10 ppm NDMA, or 10 ppm NDMA for 54 wk. No pathological changes were detected by light microscopy at 5 wk, but electron microscopy showed a marked proliferation of the smooth endoplasmic reticulum and an accumulation of inter- and perichromatin granules in the hepatocytes. Hepatic carcinomas developed

in 75% of the rats fed 10 ppm STG + 1 ppm NDMA and in 53% of those fed 10 ppm STG alone. The hepatic carcinomas were detected at 57 wk in the former group and at 60 wk in the latter. There were no hepatic carcinomas in rats fed 10 ppm NDMA alone. About 50% of the hepatic carcinomas induced by STG or STG + NDMA showed a tubular arrangement of tumor cells. Ultrastructurally, a mixture of the characteristic organelles of hepatocytes and ductular cells were frequently found in the same cells. After 54 wk, Leydig-cell tumors were detected in 47% of animals fed 10 ppm NDMA, 45% of animals fed 1 ppm STG + 10 ppm NDMA, and 15% of animals fed 10 ppm STG + 1 ppm NDMA. No metastases were observed. These results demonstrate that a low concentration of NDMA may act synergistically in STG hepatocarcinogenesis, perhaps by inducing carcinogen-activating enzymes. (21 refs)

79-1366 Carcinogen-induced Abnormalities in Rat Liver Cells and Their Modification by Chemical Agents. (Eng) Borenfreund, E. (Lab. Cell Biochemistry, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Higgins, P. J.; Steinglass, M.; Bendich, A. *Cancer Res* 39(3): 800-807; 1979.

The nature of the carcinogen-induced abnormalities in Wistar rat liver cells and the ability of certain chemicals to modify them were studied. Epithelial cells from livers of rats bearing diethylnitrosamine-induced hepatocarcinomas were propagated in vitro and cloned. These cells exhibited acentric nuclei and juxtanuclear cytoplasmic lesions indistinguishable from the Mallory hyaline bodies found in the cirrhotic livers of alcoholics. The hyaline region was comprised of a filamentous aggregate in the cytoplasm that contained components that bound concanavalin A, an interaction that was blocked by α -methylmannopyranoside. This hepatocellular aggregate also bound IgG from the sera of normal rabbits and patients with advanced alcoholic cirrhosis. The IgG fraction of sera from normal goats, rats, or mice did not show such an affinity. The morphological appearance of cells containing this Mallory body-like lesion was altered, in a reversible reaction, to one resembling normal rat liver epithelial cells after incubation with dimethyl sulfoxide or sodium butyrate. Such treatment also caused the cells to lose their acquired ability to localize concanavalin A and IgG in the juxtanuclear region. The presence of the filamentous aggregate may be responsible for the acentric displacement of the nucleus and might be correlated with the ability of the cells to express certain in vitro properties associated with the transformed state. The cytoplasmic lesion may reflect an impairment of microtubular function and polymerization. (57 refs)

79-1367 Pancreatic Ductulitis in Syrian Golden Hamsters Bearing Homologous Transplantable Pancreatic Adenocarcinomas. (Eng) Runge, R. (Epply Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105); Takahashi, M.; Pour, P. *Cancer Lett* 5(4): 225-229; 1978.

Pancreatic alterations in four Syrian hamsters that had received homologous, nonsyngeneic, transplantable, N-nitrosobis(2-oxopropyl)amine-induced pancreatic adenocarcinomas are reported. In 4/45 tumor bearers, a peculiar form of pancreatitis occurred without preferential involvement of specific pancreatic segments. It consisted of an acute inflammatory infiltrate of varying severity around or within the intralobular ductules and some islets. In some areas, there was a scant infiltration of granulocytes and in others, the ductules were essentially destroyed by a heavy infiltration of polymorphonuclear WBC. Some areas within affected organs showed no inflammation. There was no relationship between the degree or extent of inflammation and the number of tumor passages or actual size of tumors. The small blood vessels accompanying the affected ductules showed no evidence of the acute inflammation sometimes seen in Arthus-type reactions. However, all affected animals had pulmonary metastases, and the implanted tumors and metastases showed some infiltration by acute and chronic inflammatory cells. The data provide evidence that induced pancreatic neoplasms originate from ductules. (10 refs)

- 79-1368 Ductular Origin of Pancreatic Cancer and Its Multiplicity in Man Comparable to Experimentally Induced Tumors. A Preliminary Study.** (Eng) Pour, P. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB, 68105); Salmasi, S. Z.; Runge, R. G. *Cancer Lett* 6(2): 89-97; 1979.

The morphologic alterations of three randomly selected human pancreatic cancers (in men aged 45, 68, and 76) were compared with those found in Syrian hamsters after treatment with N-nitrosobis(2-oxopropyl)amine (BOP). The three human cases exhibited hyperplastic, preneoplastic, and malignant changes that were markedly multicentric and that arose predominantly from ductules, as well as from small ducts. The findings were comparable to those in the hamster model. Proliferation and malignant alterations of the intralobular ductules were commonly seen in both human and experimental tumors. The data are consistent with the concept that cells of the small ducts and, especially, of the ductules represent a potential source of human, as well as experimental, tumors. The small number of human cases studied does not allow generalization, but the marked resemblances in all three randomly selected pancreatic cancer cases were remarkable. (19 refs)

- 79-1369 Recognition of Carcinogen Damaged DNA (Meeting Abstract).** (Eng) Hart, R. W. (Ohio State Univ., Columbus, OH, 43210); D'Ambrosio, S. M. *Fed Proc* 38(3, part 1): 540; 1979. (no refs)

- 79-1370 Morphologic Differences Between Control and Nitrosomethylurea-treated Hepatocytes In Vitro (Meeting Abstract).** (Eng) Yamaguchi, M. K. (NIH, Be-

thesda, MD, 20014); Tralka, T. S.; Hanna, C. H.; Kaplan, A. E. *Fed Proc* 38(3, part 1): 579; 1979. (1 ref)

- 79-1371 Sensitive Radioimmunoassay for Detection of O⁶-Ethyldeoxyguanosine in DNA Exposed to the Carcinogen Ethylnitrosourea In Vivo or In Vitro.** (Eng) Muller, R. (Institut für Zellbiologie, Universität Essen, Hufelandstrasse 55, D-4300 Essen 1, W. Germany); Rajewsky, M. F. *Z Naturforsch C* 33(11/12): 897-901; 1978.

A radioimmunoassay was developed for the specific detection of low levels of O⁶-ethyl-2'-deoxyguanosine (EDG), a major premutational product formed in both intracellular DNA and in purified DNA in vitro after exposure to the carcinogen N-ethyl-N-nitrosourea (ENU). Antibodies directed against EDG were obtained by immunizing rabbits with a conjugate of O⁶-ethylguanosine and bovine serum albumin. Using these antibodies and ³H-labeled EDG as tracer in a competitive radioimmunoassay, 0.3 picomole of EDG were sufficient to inhibit tracer-antibody binding by 50% (antibody association constant, 7×10^8 moles⁻¹). All other alkylated DNA components analyzed exhibited considerably lower degrees of inhibition. In a sample of 130 µg of hydrolyzed DNA (equivalent to the DNA level in 2×10^7 diploid cells) EDG could be measured at a molar ratio of EDG/2'-deoxyguanosine of 3×10^{-6} , ie, about 5×10^3 EDG molecules per diploid cell. Two examples are given for the quantitation of EDG in DNA exposed to ENU in vivo or in vitro. These studies indicate the potential of immunological methods for the specific recognition of molecular structures in DNA and for the detection and quantitation of structural alterations of DNA by carcinogenic and mutagenic agents. (25 refs)

- 79-1372 Modification of L1210 Cell Nuclear Proteins by 1-Methyl-1-nitrosourea and 1-Methyl-3-nitro-1-nitrosoguanidine.** (Eng) Pinsky, S. D. (Dept. Medicine, Div. Medical Oncology, V. T. Lombardi Cancer Res. Center, Georgetown Univ. Sch. Medicine, Washington, DC, 20007); Tew, K. D.; Smulson, M. E.; Woolley, P. V. *Cancer Res* 39(3): 923-928; 1979.

Modification of the nuclear proteins of L1210 cells in culture by 1-methyl-1-nitrosourea (MNU) and 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) was examined. Preparations of radiolabeled drug were available that permitted examination of carbamylation and alkylation by MNU and of guanidination and alkylation by MNNG. Nuclear proteins were isolated from the cells following 1 hr of incubation at 37 C with 0.038-3.8 mM of ¹⁴C-labeled carcinogens. Separation of the proteins by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and Triton-acetic acid-urea gel electrophoresis yielded comparable results. All histones and many nonhistones were modified. At 0.38 mM, binding ranged from the lowest detectable level of 0.1 picomole (pmol) of [carbonyl-¹⁴C]MNU/nanomole (nmol) of H4 (carbamylation) to 13.1 pmol [methyl-¹⁴C]MNNG/nmol H2A. MNNG was approx 12 times as potent as MNU at that

concentration, and it showed more binding than MNU at all doses for both types of reactions. H1 was more strongly guanidinated than the other histones (11.0 pmol/nmol at 0.38 mM), but H2B and H3 were the major targets of carbamoylation (0.9 and 118 pmol/nmol, respectively, at 0.38 mM). With both drugs, methylation of H1 and H2A was most marked. Generally, there was twice as much binding to acid-soluble nonhistones. The results show that nuclear proteins are modified upon exposure to MNU and MNNG. (30 refs)

- 79-1373 Neoplasms in Rats and Mice Fed Butylurea and Sodium Nitrite Separately and in Combination.** (Eng) Murthy, A. S. (EG&G Mason Res. Inst., Worcester, MA, 01508); Baker, J. R.; Smith, E. R.; Zepp, E. *Int J Cancer* 23(2): 253-259; 1979.

Fischer 344 rats and C57BL/6 mice were fed 0.58% butylurea and/or 0.50% sodium nitrite mixed in the diet for 365 days, followed by 120 days on a stock diet. The number and type of neoplasms were not significantly increased in either species receiving butylurea or sodium nitrite alone. Feeding the two chemicals simultaneously induced neoplasms of the lung, Zymbal's gland, forestomach, intestine, and hemopoietic tissues in rats and malignant lymphomas in mice. Tumor incidence was increased from control values for male and female rats of 60% and 45%, respectively, to 93% and 98%; the increase in male and female mice was from control values of 8% and 18%, respectively, to 90% and 67%. The increased incidence of neoplasms in rats and mice fed butylurea plus sodium nitrite may result from in vivo formation of the carcinogen N-butyl-N-nitrosourea. (37 refs)

- 79-1374 Effects of Iodine Deficiency and High-Fat Diet on N-Nitrosomethylurea-induced Mammary Cancers in Rats.** (Eng) Cave, W. T. (Div. Endocrinology, Dept. Internal Medicine, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY, 14611); Dunn, J. T.; MacLeod, R. M. *Cancer Res* 39(3): 729-734; 1979.

The effects of dietary iodine and fat on the development of N-nitrosomethylurea (NMU)-induced mammary tumors were studied in female Buffalo, Wistar-Furth, and Fischer rats. NMU (5 mg/100 g) was administered iv to 50-day-old rats, with two subsequent injections given 4 and 8 wk later. The animals were maintained on a standard diet containing 4.63% fat and 1.1 to 1.4 ppm iodine, a special diet (LIHF) containing 11.8% fat and <0.1 ppm iodine, an iodine-supplemented (1.6 ppm) LIHF diet, or an iodine-supplemented, vitamin-deficient LIHF diet. The number of tumors and the tumor mass were larger in the animals given the supplemented or unsupplemented LIHF diet than in those given the standard diet. Enlargement of the kidney, liver, and spleen was evident in the groups with the greatest tumor growth, but there was little evidence of altered pituitary function in these animals. Ovariectomy following the last dose of NMU prevented the accelerated tumor growth in the animals given

the LIHF diets. Ovariectomy also led to a significant depression in thyroid-stimulating hormone (TSH) and prolactin (PRL) production in vitro, and to a less significant decrease in serum PRL. The data indicate that iodine deficiency did not significantly promote NMU carcinogenesis and that estrogens may directly influence TSH synthesis in vivo. (30 refs)

- 79-1375 An Experimental Model for Peripheral Nerve Tumours in Monkeys.** (Eng) Dimant, J. N. (Institute Oncology and Radiology, Ministry of Health of the Uzbekian SSR, Tashkent, USSR); Beniashvili, D. S. *J Med Primatol* 7(5): 324-329; 1978.

Tumor induction was studied in five *Macaca mulatta* monkeys treated with methylnitrosourea (MNU: 15 iv injections of 20 mg/kg over 3 mo) and in seven monkeys treated with MNU + antigen from the homologous tissue of the sciatic nerve from another *Macaca mulatta* monkey (introduced with Freund's complete adjuvant into the interscapular space a total of 6 times starting 2 wk after the second MNU injection). The total dose of MNU ranged from 840 to 1,350. The monkeys were observed for 3 yr. Circumscribed benign neurinomas attached to the trunk of the sciatic nerve were found in 3/7 animals treated with MNU + antigen. The first palpable tumor was found 15 mo after the beginning of the experiment, and all animals with induced neurogenic tumors showed partial distortion of sciatic nerve conduction, as manifested by paresis of the muscles innervated by this nerve. The induced peripheral nerve tumors were similar in pathology, biologic properties, and clinical manifestations to the human tumors. No tumors were found in animals treated with MNU alone. The results suggest that organospecific immunization aids in the initiation and stimulation of MNU-induced neoplasia in the peripheral nervous system. (3 refs)

- 79-1376 Rifampicin as a Spectroscopic Probe of the Mechanism of *E. Coli* RNA Polymerase (Meeting Abstract).** (Eng) Reisbig, R. (Dept. Biochemistry, Colorado State Univ., Fort Collins, CO, 80523); Woody, A. Y.; Woody, R. W. *Biophys J* 25(2, part 2): 221a; 1979. (no refs)

- 79-1377 Nitrosamine Formation from Interaction of Cardiovascular Drugs (Meeting Abstract).** (Eng) Raisfeld, I. H. (State Univ. New York, Stony Brook, NY, 11594); Lin, C.; Cheng, J.; Brandys, J. *Fed Proc* 38(3, part 1): 680; 1979. (1 ref)

- 79-1378 Carcinogenesis Bioassay of Technical-Grade Piperonyl Butoxide in F344 Rats.** (Eng) Cardy, R. H. (Dept. Pathology, Litton Bionetics, 5516 Nicholson Lane, Kensington, MD, 20795); Renne, R. A.; Warner, J. W.; Cypher, R. L. *J Natl Cancer Inst* 62(3): 569-578; 1979.

The results of a 2-yr carcinogenesis bioassay of the insecticide synergist piperonyl butoxide, α -[2-(2-butoxyethoxy)]-4,5-methylenedioxy-2-propyltoluene, in inbred F344 rats are reported. Doses of 10,000 and 5,000 ppm of the compound were administered continuously in the feed. Although a statistically significant dose-related increase in the incidence of lymphoreticular neoplasia occurred in females, the incidence of this class of neoplasm was higher in control males than in treated males. The finding of statistical significance in one sex is not sufficient evidence of a biologic effect to justify an indictment of carcinogenic action. However, inasmuch as the chief use of this substance is to alter the *in vivo* metabolism of other chemicals, its possible role as a cocarcinogen should be carefully considered in any risk-benefit evaluation aimed at settling policies regarding its uses. (16 refs)

- 79-1379 The Effect of Nitrofurans on Mitosis, Chromosome Breakage and Sister-Chromatid Exchanges in Human Peripheral Lymphocytes.** (Eng) Cohen, M. M. (Dept. Human Genetics, Hadassah Hebrew Univ. Medical Center, Jerusalem, Israel); Sagi, M. *Mutat Res* 59(1): 139-142; 1979.

The effects of two antimicrobial nitrofurans, 3-amino-6-[2-(5-nitro-2-furyl)vinyl]pyridazine (Carofur, CF) and 3-(5-nitrofurylideneamino)-2-oxazolidone (Furazolidone, FZ), on cell division, chromosome breakage, and the induction of sister-chromatid exchanges were studied in cultured human peripheral lymphocytes. Both compounds (0.2, 2.0, and 20.0 $\mu\text{g}/\text{ml}$) produced dose-dependent mitotic suppression, chromosome breakage, and sister-chromatid exchanges; these changes were more pronounced with FZ. Statistically significant differences ($p < 0.001$) in sister-chromatid exchange frequency were noted when controls and treated cells were compared. Differential staining was absent at the highest CF dose, possibly as a result of a long mitotic delay of the sensitive S cells. (22 refs)

- 79-1380 Sterigmatocystin-DNA Interactions: Identification of a Major Adduct Formed after Metabolic Activation In Vitro.** (Eng) Essigmann, J. M. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139); Barker, L. J.; Fowler, K. W.; Francisco, M. A.; Reinhold, V. N.; Wogan, G. N. *Proc Natl Acad Sci USA* 76(1): 179-183; 1979.

The metabolic activation and DNA binding of sterigmatocystin (ST), a potent hepatocarcinogen, were investigated. ST was covalently bound to calf thymus DNA by incubation in the presence of phenobarbital-induced rat liver microsomes. Acid hydrolysis of ST-modified DNA liberated a major guanine-containing adduct, present in DNA at an estimated level of 1 ST residue/100-150 nucleotides. The adduct was isolated by high-pressure liquid chromatography and subjected to structural analysis. Spectral and chemical data identified the adduct as 1,2-dihydro-2-(N'-guanyl)-1-hydroxysterigmatocystin, the guanine and hydroxyl moieties being in a trans

configuration. The structure and stereochemistry of this adduct indicated that the *exo*-ST-1,2-oxide was the metabolite that reacted with DNA, and the quantitative yield of adduct indicated that this metabolite was a major product of the *in vitro* metabolism of ST. (37 refs)

- 79-1381 Carcinogenicity of Di(N-nitroso)-perhydropyrimidine (DNPP) after Intraperitoneal Application to Rats.** (Eng) Bertram, B. (Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Heidelberg, W. Germany); Habs, M.; Wiessler, M.; Braun, H.; Kretzer, H. *Cancer Lett* 6(1): 57-60; 1979.

The carcinogenicity of di(N-nitroso)perhydropyrimidine (DNPP) was assessed in male Sprague-Dawley rats. The rats received 30 mg/kg (group 1) or 15 mg/kg (Group 2) DNPP ip 1x/wk for life. DNPP treatment significantly reduced the life expectancy in both groups. At 34 wk after the start of treatment, survivors included 13% of Group 1 and 0% of Group 2 vs 93% of controls. The median survival of Groups 1 and 2 was 51 and 156 days, respectively. DNPP induced both benign and malignant tumors of the esophagus (27% incidence in Group 1, 33% in Group 2) and possibly also of the liver (4% incidence in Group 1, 8% in Group 2). No tumors were found in controls. (9 refs)

- 79-1382 Mutation Induction by 5-Fluorodeoxyuridine in Synchronous Chinese Hamster Cells.** (Eng) Aebersold, P. M. (Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720). *Cancer Res* 39(3): 808-810; 1979.

The mutagenicity of 5-fluorodeoxyuridine (FUdR: 0.2 $\mu\text{g}/\text{ml}$) to Chinese hamster ovary cells synchronized by mitotic detachment was studied. In synchronous cultures treated with FUdR (0.2 $\mu\text{g}/\text{ml}$ for 1 hr at various times after mitotic detachment), there was a peak of induced 6-thioguanine (6-TG) resistance about 8 hr after mitotic detachment. FUdR treatment (0.2 $\mu\text{g}/\text{ml}$) of cells synchronized at the G₁-S boundary with hydroxyurea did not significantly affect colony formation or plating efficiency at the time of 6-TG selection. Although 2.0 $\mu\text{g}/\text{ml}$ FUdR reduced colony formation only slightly, the colonies were less than one-half the diameter of untreated colonies and the plating efficiency of cells at the time of 6-TG selection was reduced by 75%. FUdR (0.2 $\mu\text{g}/\text{ml}$) was not significantly mutagenic in asynchronous cells. A total of 24 6-TG-resistant colonies were observed on five plates of synchronized cells treated with FUdR alone, but only 1 6-TG-resistant colony was observed on five plates treated with FUdR + 10^{-4} M thymidine. The data suggest that FUdR treatment leads to mutagenesis at the growing points of DNA replication. (11 refs)

- 79-1383 N⁶(Methylnitroso)adenosine: A Carcinogenic Nitrosamine Derived from a Naturally-occurring Nucleoside.** (Eng) Giner-Sorolla, A. (Walker Lab., Memorial Sloan-Kettering Cancer Center, Rye, NY, 10580);

Greenbaum, J. H.; Last-Barney, K.; Anderson, L. M.; Budinger, J. M. *Cancer Lett* 6(2): 79-82; 1979.

The carcinogenicity of N⁶(methylnitroso)adenosine [M⁶(NO)Ado], the nitrosated derivative of the naturally occurring modified nucleoside N⁶-methyladenosine, was tested in Swiss mice. Pregnant females were injected on days 15, 17, and 19 of gestation; their offspring were injected on days 4, 7, and 10 and then, starting on day 21, 3x/wk for 12 wk (all at 40 mg/kg ip). In the injected mice, 84% of the females and 44% of the males died with thymic lymphomas between 12 and 36 wk of age. Primary lung tumors were found in 71% of these females and in 58% of the males. Liver tumors were found in 33% of the treated male mice at 1 yr of age compared with 17% of the controls; none were found in treated females. The high incidence of tumors in three different tissues following M⁶(NO)Ado treatment strongly suggests direct carcinogenesis, although an increase in spontaneous tumors as a result of indirect effects cannot be ruled out. It is suggested that M⁶(NO)Ado be included in considerations of carcinogenic nitrosamines in food and in the gastrointestinal tract. (9 refs)

79-1384 Biliary Excretion of [¹⁴C]Penicillic Acid by Rats. (Eng) Park, D. L. (Office Health Affairs, Food and Drug Admin., Washington, DC, 20204); Brouwer, E.; Heath, J. L. *J Toxicol Environ Health* 4(1): 9-13; 1978.

A study of the biliary excretion of ¹⁴C-penicillic acid in male rats using straight and recycle cannulation techniques demonstrated that the radioactivity level in bile was five times greater with straight cannulation. Variability of the level of radioactivity was much less with the recycle technique than with straight cannulation. The biological half-retention life for ¹⁴C-penicillic acid in bile was 3.63 hr. (9 refs)

79-1385 Production of Sister Chromatid Exchanges by Various Cancer Chemotherapeutic Agents. (Eng) Banerjee, A. (Div. Hematology-Oncology, Dept. Medicine, Children's Hosp. Los Angeles, Los Angeles, CA, 90027); Benedict, W. F. *Cancer Res* 39(3): 797-799; 1979.

Various cancer chemotherapeutic agents were tested for their ability to produce increases in sister chromatid exchanges (SCE's) in cloned hamster A(T₁)C1-3 cells. The two alkylating agents melphalan and thiotepa [tris(1-aziridinyl)phosphine sulfide] produced significant dose-dependent increases in SCE's, the former at doses as low as 0.005 µg/ml and the latter at doses as low as 0.01 µg/ml. Actinomycin D and bleomycin were significantly less efficient in inducing SCE's. The antimetabolite methotrexate significantly increased SCE's at a concentration of 0.1 µg/ml, whereas 6-mercaptopurine was ineffective even at 1.0 µg/ml. Hycanthone at 1.0 µg/ml and 5-azacytidine at 2.5 µg/ml produced three-fold increases in SCE's. Tilorone did not increase the frequency of SCE's even at 5 µg/ml. Determination of increases in SCE production may be an additional sensitive

method for detecting potential mutagenic and/or oncogenic agents in the environment. (15 refs)

79-1386 Mutagenicity and Mutagenic Specificity of Metronidazole and Niridazole in *Neurospora crassa*. (Eng) Ong, T. (Natl. Inst. Occupational Safety and Health, ALOSH, Morgantown, WV, 26505); Slade, B. *J Toxicol Environ Health* 4(5/6): 815-824; 1978.

Mutagenicity and mutagenic specificity studies of niridazole and metronidazole in the adenine-3 test system of *Neurospora crassa* demonstrated that neither is mutagenic in resting conidia, but that both are mutagenic in the growing vegetative cells. The genetic alterations induced by metronidazole were similar to those induced by several monofunctional alkylating agents. Niridazole induced predominantly base-pair substitution mutations. (27 refs)

79-1387 Mechanism of N-Nitrosopyrrolidine Formation in Bacon. (Eng) Bharucha, K. R. (Canada Packers Ltd., Toronto, Ontario, Canada, M6N 1K4); Cross, C. K.; Rubin, L. J. *J Agric Food Chem* 27(1): 63-69; 1979.

Experiments demonstrate that N-nitrosopyrrolidine in cooked bacon arises by decarboxylation of N-nitrosoproline, which is probably formed by radical nitrosation of free proline in the pork belly. A method for measuring N-nitrosoproline in raw bacon is described. It demonstrated that raw bacon is essentially free of volatile nitrosamines. (37 refs)

79-1388 Malignant Transformation In Vitro by Tryptophan Pyrolysis Products. (Eng) Takayama, S. (Dept. Experimental Pathology, Cancer Inst., 1-37-1, Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan); Hirakawa, T.; Sugimura, T. *Proc Jpn Acad Ser B* 54(7): 418-422; 1978.

In vitro hamster embryo cells underwent malignant transformation after treatment with tryptophan pyrolysis products and 3-methylcholanthrene. When the cells were inoculated into hamster cheek pouches, small nodules were seen within a week. The tumors consisted of pleomorphic fibroblastic cells, and they appeared to be anaplastic fibrosarcomas. (9 refs)

79-1389 The Effect of L-Tryptophan and Certain Other Amino Acids on Liver Nitrosodimethylamine Demethylase Activity. (Eng) Evarts, R. P. (Carcinogen Metabolism and Toxicology Branch, NCI, Bethesda, MD, 20014); Mostafa, M. H. *Food Cosmet Toxicol* 16(6): 585-589; 1978.

The effect of the amino acids L-tryptophan, L-cysteine, L-methionine, L-tyrosine, and L-glycine on liver nitrosodimethylamine-demethylase (NDMA-demethylase) ac-

tivity was studied in male Wistar rats. Each amino acid was fed at a level of 1% of the diet to weanling rats for 12 days. L-Tryptophan increased liver NDMA-demethylase activity significantly above that of control animals, but L-cysteine had the opposite effect. The other amino acids did not alter enzyme levels. L-tryptophan was effective when it was given to young rats for 6 or 12 days and the animals were killed at the age of 27 or 35 days. When the effect of the duration of tryptophan feeding (3-47 days) and at the age of the animals (21-51 days) were taken into account, a 6-day feeding schedule had the highest activating effect on liver NDMA-demethylase (30% above control values). The highest activation (180%) was obtained when the 6-day period of tryptophan feeding was started at age 27 days and the animals were killed at the age of 33 days. The highest enzyme activities were always associated with a high liver wt:body wt ratio. Other reports have indicated that a low-protein diet protects against toxicity and a high-protein diet against carcinogenicity. The fact that tryptophan and cysteine affect the activity of microsomal enzymes indicates that the amino acid composition of the diet is important in determining the toxicity and carcinogenicity of foreign compounds. (33 refs)

- 79-1390** Microsomal Biphenyl 2-Hydroxylation in the Presence of Some Carcinogenic Alkylaryltriazenes. (Eng) McPherson, F. (Smith Kline and French Labs., Ltd., Welwyn Garden City, Herts, England); Kolar, G. F. *Cancer Lett* 6(1): 33-38; 1979.

A hepatic mixed-function oxygenase system, which gave enhanced biphenyl 2-hydroxylation in the presence of known carcinogens in vitro, was tested as a short-term assay for the detection of dangerous compounds using eight carcinogenic triazenes: 3,3-dimethyl-1-phenyltriazene, 3-methyl-1-phenyltriazene, 1-(4-bromophenyl)-3,3-dimethyltriazene, 1-(2,4,6-tribromophenyl)-3,3-dimethyltriazene, 1-(2,4,6-tribromophenyl)-3-methyltriazene, 1-(4-chlorophenyl)-3,3-dimethyltriazene, 1-(2,4,6-trichlorophenyl)-3,3-dimethyltriazene, and 1-(2,4,6-trichlorophenyl)-3-methyltriazene. The test triazene (0.5 mg in 0.5 ml groundnut oil) was added to hepatic microsomes prepared from adult male Wistar rats, and the mixture was preincubated 10 min in the presence of an NADPH-generating system. Biphenyl was then added, and the incubation was continued for 5 min. 2- and 4-hydroxybiphenyls were extracted and determined fluorimetrically. Preincubation of the test system with 20-methylcholanthrene or with safrole significantly enhanced biphenyl 2-hydroxylation (380% and 193%, respectively, compared with 100% in controls). However, preincubation of the system with any of the triazenes did not enhance biphenyl 2-hydroxylation. The results indicate that the biphenyl test is not successful with triazene compounds. It is not known whether these carcinogens interfere with the fluorimetric methodology or whether each triazene or its cleavage product and/or metabolite specifically interferes with hydroxylation of the biphenyl substrate. (15 refs)

- 79-1391** Mutagenicity of Metronidazole (Letter to Editor). (Eng) Hartley-Asp, B. (Aktiebolaget Leo Res. Labs., S-251 00 Helsingborg, Sweden). *Lancet* 1(8110): 275; 1979.

Chromosome analysis in 12 patients receiving metronidazole (MN) therapy for vaginal trichomoniasis (200 mg 3x/day for 7 days) revealed no increase in any chromosomal aberration type. However, the range of chromatid aberrations during and after treatment was larger than that before treatment; this was due to a pronounced increase found in two patients, one during and the other after treatment. These studies indicate MN does not have chromosome-breaking activity during the short-term treatment for vaginal trichomoniasis. (8 refs)

- 79-1392** Actions of an Antispermatic, but Non-mutagenic, Indenopyridine Derivative in Mice and *Salmonella typhimurium*. (Eng) Matter, B. E. (Biological and Medical Res. Div., Sandoz Ltd., Basel, Switzerland); Jaeger, I.; Suter, W.; Tsuchimoto, T.; Deyssenroth, H. *Mutat Res* 66(2): 113-127; 1979.

Following single po administration to CD-1 mice, the indenopyridine derivative (4aRS,5SR,9bRS)-2-ethyl-1,3,4,4a,5,9b-hexahydro-7-methyl-1-5-p-tolyl-2H-indeno(1,2-c)pyridine hydrochloride produced long-lasting inhibition of spermatogenesis at dose levels of 10 mg/kg and higher. Testes wts were reduced from days 2 to 217 after treatment, and males showed partial or total sterility at 3-6 wk following treatment, with full recovery at 7-29 wk. The compound showed no indications of dominant lethality or mutagenic potentiality. (14 refs)

- 79-1393** Karyotype and Tumorigenicity of 1-Methylguanine-transformed Chinese Hamster Cells. (Eng) Trewyn, R. W. (Dept. Biochemistry, Univ. Colorado Medical Center, Denver, CO, 80262); Kerr, S. J.; Lehman, J. M. *J Natl Cancer Inst* 62(3): 633-638; 1979.

Chinese hamster embryo cells transformed with the transfer RNA catabolite 1-methylguanine were characterized by Giemsa-banded karyotyping and by their tumorigenic potency in athymic nude mice (10^6 cells sc into each flank). All seven 1-methylguanine-transformed cell lines were hyperdiploid with a modal chromosome number of 23. Three of these lines had an additional marker chromosome derived from the long (q) arm of chromosome 4, and they had alterations of chromosome 5 as well. Two of these three cell lines were tumorigenic. Nonrandom chromosome changes were observed in the other four transformed cell lines, and these changes included the addition of all or a portion of chromosome 6. One of these cell lines was also tumorigenic in nude mice. The three tumorigenic lines gave rise to fibrosarcomas or histiocytomas with local invasion and no evidence of metastasis within 2-6 wk. Specific cytogenetic changes were observed in most of the 1-methylguanine-transformed popu-

lations, in contrast to the karyotypic heterogeneity of a benzo(a)pyrene-transformed cell line. (11 refs)

- 79-1394 Enhancement of Gastric Carcinogenesis in Dogs Given N-Methyl-N'-nitro-N-nitrosoguanidine Following Vagotomy.** (Eng) Fujita, M. (Dept. Oncologic Surgery, Res. Inst. Microbial Diseases, Osaka Univ., Yamada-kami, Suita, Osaka 565, Japan); Takami, M.; Usugane, M.; Nampei, S.; Taguchi, T. *Cancer Res* 39(3): 811-816; 1979.

An attempt was made to improve the induction of gastric cancer in dogs by performing selective vagotomy (Va-x) without the gastric drainage procedure before administration of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Twenty dogs were divided into two groups of 10 dogs (5 beagles and 5 mongrels). The control group received MNNG alone. The experimental group was vagotomized 2 mo before administration of MNNG. MNNG soln (50 µg/ml) was administered in the drinking water for 12 mo. In the vagotomized group, gastric adenocarcinomas were induced in all of eight effective dogs, whereas in the control group they were seen in 6/8 dogs. The gastric cancer was multiple in many dogs, but most of the lesions remained in the early stage. The total number of tumors induced in the Va-x and control groups was 42 and 16, respectively. Va-x resulted in the production of more-advanced cancers. One lesion in the control group and four in the Va-x group were advanced cancers invading the serosa. Advanced gastric cancers with metastases to the liver, lymph nodes, and lungs developed exclusively in two vagotomized dogs. Gastric acid secretion of the vagotomized dogs, measured after termination of MNNG was reduced to an av of one-fourth that of the controls. The possible role of Va-x in the enhancement of gastric carcinogenesis in dogs by MNNG is discussed in terms of the inactivation of MNNG in gastric juice and the ulcerogenic action of the carcinogen in the gastric mucosa. (18 refs)

- 79-1395 Volatile N-Nitrosamines in the Urine of Normal Donors and of Bladder Cancer Patients.** (Eng) Kakizoe, T. (Urology Div., Natl. Cancer Center Hosp., 5-1-1 Tsukiji, Chuo-ku, Tokyo 104, Japan); Wang, T. T.; Eng, V. W.; Furrer, R.; Dion, P.; Bruce, W. R. *Cancer Res* 39(3): 829-832; 1979.

Urine samples from 27 male donors and 4 bladder cancer patients were analyzed for the presence of volatile N-nitrosamines by gas-liquid and high-pressure liquid chromatography interfaced to a thermal energy analyzer. Of 50 samples from normal men, 10 contained nitrosodimethylamine (0.02-0.10 µg/liter), 6 contained nitrosodiethylamine (0.02-3.10), 9 contained nitrosomorpholine (0.06-0.67), and none contained nitrosodibutylamine. Of four samples from the bladder cancer patients, two contained nitrosodimethylamine (0.32 and 0.70) and nitrosodibutylamine (0.35 and 0.66). Two had no nitrosamines in their urine samples. Cigarette smoking did not appear to be related to the pattern or amount of urinary volatile

N-nitrosamines. The possibility that the N-nitrosamines arise from the diet or from endogenous sources is considered. (19 refs)

- 79-1396 Elevation of Extrahepatic Glutathione S-Transferase and Epoxide Hydratase Activities by 2(3)-tert-Butyl-4-hydroxyanisole (BHA) (Meeting Abstract).** (Eng) Benson, A. M. (Dept. Pharmacology, Johns Hopkins Medical Inst., Baltimore, MD, 21205); Cha, Y. N.; Bueding, E.; Heine, H. S.; Talalay, P. *Fed Proc* 38(3, part 1): 506; 1979. (no refs)

- 79-1397 Photomutagenesis by Chlorinated Phenothiazine Tranquilizers.** (Eng) Jose, J. G. (Sch. Optometry, Univ. California, Berkeley, CA, 94720). *Proc Natl Acad Sci USA* 76(1): 469-472; 1979.

Several chlorinated and nonchlorinated phenothiazines were assayed for mutagenicity in the *Salmonella typhimurium* test system with and without exposure to near-UV irradiation. All of the chlorinated derivatives tested (chlorophenothiazine, chlorpromazine, compazine, and perphenazine) were mutagenic with irradiation, but the nonchlorinated derivatives were not. None of the phenothiazines were mutagenic in the dark. The most reactive phenothiazine was chlorpromazine, which was further analyzed with several different *Salmonella* strains to characterize the nature of the photoinduced mutagenicity. Mutagenicity was observed only in strains that lacked excision repair of DNA (eg, strains TA2637 and TA1537), and it was elevated in strains that contained the plasmid pKM101 (TA2637), which may enhance error-prone repair. Similar strain sensitivity was observed with Compazine. Based on these findings and the relationship between mutagenesis and cancer, it is suggested that the nonchlorinated phenothiazine derivatives be used for medical purposes whenever possible. (29 refs)

- 79-1398 Hematotoxicity of Inhaled Benzene to Sprague-Dawley Rats and AKR Mice at 300 ppm.** (Eng) Snyder, C. A. (A. J. Lanza Labs., New York Univ., Inst. Environmental Medicine, Tuxedo, NY, 10987); Goldstein, B. D.; Sellakumar, A.; Wolman, S. R.; Bromberg, I.; Erlichman, M. N.; Laskin, S. *J Toxicol Environ Health* 4(4): 605-618; 1978.

Sprague-Dawley rats exposed to 300 ppm benzene vapor for 6 hr/day, 5 days/wk, for life exhibited lymphocytopenia, mild anemia, and moderately decreased survival. AKR/J mice exposed to the same regimen showed severe lymphocytopenia and anemia accompanied by granulocytosis and reticulocytosis. Survival and wt gain were also significantly decreased. No indications of a leukemic or preleukemic response were observed in either species. (35 refs)

- 79-1399 Effect of Hexestrol on the Breast of Menopausal Women.** (Ger) Kubista, E. (I. Univer-

sitats-Frauenklinik, Spitalgasse 23, A-1090 Vienna, Austria); Grunberger, W.; Wolf, G. *Wien Med Wochenschr* 129(1): 16-19; 1979.

The effect on the breast of hexestrol substitution therapy (50 mg im for ≥ 12 mo) after ovariectomy and hysterectomy was studied in 167 menopausal women (av age 46.6 yr) over a 2.5-yr period. One hundred and seventy-nine untreated menopausal women (av age 47.9 yr) served as controls. Mammography and thermography revealed no differences between the two groups. Adenomatosis was found in two patients in the control group, but in none of the treated patients. Hexestrol treatment caused no changes in blood clotting compared with controls. The findings indicate that hexestrol is acceptable for substitution therapy in menopause. (16 refs)

- 79-1400 Cytospectrophotometric Investigation of Cytoplasmic RNA in Regenerating and Neoplastic Livers.** (Fre) Moulin-Camus, M. C. (Institut du cancer de Montreal, Centre hospitalier Notre-Dame, Montreal, Quebec, Canada); Daoust, R. *Rev Can Biol* 37(4): 235-255; 1978.

A quantitative cytospectrophotometric investigation was made of cytoplasmic hyperbasophilia in the foci of neoplastic transformation and hepatic tumor cells of male Wistar rats fed a protein-free diet containing 4-dimethylaminoazobenzene (DAB: 0.06% of diet) for 120-150 days, and in the regenerating liver of normal rats subjected to partial hepatectomy. The cells were stained with methylene blue. The two-fold increase in the dye-binding capacity of the cytoplasmic RNA of the tumor cells and neoplastic foci was found to be primarily due to a qualitative alteration resulting in an increased affinity for basic dyes and to an increase in the nuclear-cytoplasmic ratio. This type of hyperbasophilia differed radically from the weak variations in basophilia observed in normal regenerating liver and the hyperplastic liver parenchyma of the DAB-treated rats. In these cases, the changes appeared to be related mainly to de novo RNA synthesis. Biochemical assays of cellular fractions indicated that ribosomes are the organelles responsible for the hyperbasophilic properties of hepatocytes in areas of neoplastic transformation. (51 refs)

- 79-1401 Impairment of Tyrosine Aminotransferase Induction by Hydrocortisone in the Liver of Rats Treated with o-Aminoazotoluene.** (Rus) Kaledin, V. I. (Inst. Cytology and Genetics, Novosibirsk, USSR); Glazko, T. T.; Zakharova, N. P. *Dokl Akad Nauk SSSR* 244(1): 233-237; 1979.

The effect of the carcinogenic dye o-aminoazotoluene (OAT) on hydrocortisone-induced tyrosine aminotransferase (TAT) activity was studied in 2- to 3-mo-old DD and CC57BR mice. DD mice are sensitive to the hepatocarcinogenic effect of OAT and CC57BR mice are resistant. Animals were inoculated ip with OAT and, 20 hr later, with hydrocortisone (2.5 or 12.5 mg/100 g). Hydrocortisone alone increased TAT ac-

tivity: 5 hr after injection with 2.5 mg/100 g, there was a 4.6-fold increase in DD mice and a 3.5-fold increase in CC57BR mice. OAT caused a 1.75-fold decrease of TAT induction in DD mice and a 1.2-fold decrease in CC57BR mice. (15 refs)

- 79-1402 Chromatin-Associated Low Molecular Weight RNA Released into the Liver Cytoplasm in Rats Fed 3'-Methyl-4-dimethylaminoazobenzene (3'-MeDAB) (Meeting Abstract).** (Eng) Patel, N. T. (Univ. Texas Medical Branch, Galveston, TX, 77550); Holoubek, V. *Fed Proc* 38(3, part 1): 499; 1979. (no refs)

- 79-1403 Betel Nuts, Arecaidine, and Oral Cancer (Letter to Editor).** (Eng) Ashby, J. (Central Toxicology Lab., Imperial Chemical Industries, Ltd., Alderley Park, Macclesfield, Cheshire SK10 4TJ, England); Styles, J. A.; Boyland, E. *Lancet* 1(8107): 112; 1979.

The results of an in vitro assay of the carcinogenicity of arecaidine and arecoline, which are present in betel nuts, are reported. Both alkaloids gave an almost identical positive response in a cell-transformation assay, underlining their apparent bioequivalence. (9 refs)

- 79-1404 Metabolism of Drugs and Carcinogens in Man: Antipyrine Elimination as an Indicator.** (Eng) Kalamegham, R. (Natl. Inst. Nutrition, Indian Council Medical Res., Jamai Osmania P.O., Hyderabad 500 007, A. P., India); Krishnaswamy, K.; Krishnamurthy, S.; Bhargava, R. N. *Clin Pharmacol Ther* 25(1): 67-73; 1979.

The suitability of antipyrine (AP) in predicting drug and carcinogen metabolism was investigated by studying the in vivo AP elimination rate (K_e) and the in vitro metabolism of drugs and carcinogens in liver preparations in the same individual. The test subjects were 20 men with chronic duodenal ulcer that were scheduled for gastrojejunostomy. Most of the men smoked cigarettes or beedies (tobacco rolled in dry leaves); none took any alcohol during the previous year. The half-life and K_e of AP were determined by linear regression analysis in all subjects prior to surgery. AP (18 mg/kg) was administered under fasting conditions, and plasma levels 4, 6, 9, and 12 hr later were determined spectrophotometrically. Both the in vitro enzyme activities and the K_e showed wide variations. Significant correlations were observed only between aryl hydrocarbon hydroxylase (AHH) activity and AP K_e ($p < 0.05$), aniline hydroxylase activity ($p < 0.001$), and γ -glutamyl transferase activity ($p < 0.01$). Aminopyrine N-demethylase did not correlate with any of the parameters studied. Although the degree of correlation between AP K_e and AHH was statistically significant, it was not satisfactory for predictive purposes. This study points out some of the problems and limitations of in vivo-in vitro comparisons and it confirms earlier doubts on the usefulness of AP as a proto-

type drug for predicting drug and carcinogen metabolism in humans. (30 refs)

79-1405 Cellular Localization of Nicotine in Bronchial Epithelium of Mice (Meeting Abstract). (Eng)

Waddell, W. J. (Dept. Pharmacology, Univ. Louisville, Louisville, KY, 40201); Marlowe, C. *Fed Proc* 38(3, part 1): 584; 1979. (3 refs)

79-1406 Epoxide Intermediates in the Metabolism of Naphthalene (Meeting Abstract). (Eng)

Stillwell, W. G. (Baylor Coll. Medicine, Houston, TX, 77030); Horning, M. G.; Hill, R. M.; Griffin, G. W. *Fed Proc* 38(3, part 1): 585; 1979. (no refs)

79-1407 Mutagenicity of 19 Major Graphic Arts and Printing Dyes. (Eng)

Milvy, P. (Environmental Sciences Lab., Mount Sinai Sch. Medicine, City Univ. New York, New York, NY, 10029); Kay, K. *J Toxicol Environ Health* 4(1): 31-36; 1978.

The mutagenicity of 19 dyes, representative of those used most extensively in the graphic arts and printing industry and for which no carcinogenic data exist, was tested in *Salmonella typhimurium* strains TA98, TA1538, and TA1535, with and without microsomal activation. The microsomes were prepared from Aroclor 1254-induced male Swiss Webster mice. Two of the 19 dyes were weakly mutagenic. Para Red, a derivative of 1-phenylazonaphthalene, was mutagenic with microsomal activation and Dinitroaniline Orange, a derivative of azobenzene, was directly mutagenic. Both dyes were frameshift mutagens; their planar aromatic structure probably permits them to complex with the DNA double helix. It is suggested that the carcinogenic potential of these two dyes be evaluated in animal studies. (5 refs)

79-1408 Evidence for the Absence of a Mutagenic Effect of Methadone in Germ Cells of *Drosophila melanogaster*. (Eng)

Zimmering, S. (Div. Biology and Medicine, Brown Univ., Providence, RI, 02912). *Mutat Res* 66(2): 133-134; 1979.

Mutagenicity studies revealed that methadone (0.1 or 1.0 mg/ml) produced no sex-linked recessive lethals when either fed to or injected in adult male *Drosophila melanogaster*. Similarly, the results of tests for chromosome breakage and nondisjunction gave no evidence of a mutagenic effect. (no refs)

79-1409 Transfer of Polychlorinated Biphenyls from Mothers to Foetuses and Infants. (Eng)

Masuda, Y. (Daiichi Coll. Pharmaceutical Sciences, Minami-Ku, Fukuoka 815, Japan); Kagawa, R.; Kuroki, H.; Kuratsune, M.; Yoshimura, T.; Taki, I.; Kusuda, M.; Yamashita, F.; Hayashi, M. *Food Cosmet Toxicol* 16(6): 543-546; 1978.

The transfer of polychlorinated biphenyls (PCB's) through the placenta and maternal milk was studied by analyzing blood, milk, adipose tissue, and other tissues from mothers, fetuses, and infants for PCB's. PCB levels in maternal blood were approx four-fold higher than those in cord blood. PCB levels in the maternal blood were weakly correlated with those in cord blood and strongly correlated with those in maternal adipose tissue. However, the correlation coefficient between maternal adipose tissue and cord blood samples was not significant. PCB levels in blood samples from infants were significantly higher than those in the maternal blood, the maternal blood levels being significantly correlated with those in the fat in the maternal milk. PCB levels in infant blood were not significantly correlated with those in the maternal blood or milk. PCB concentrations in the adipose tissue, liver, and adrenals from stillborn infants were less than one-tenth of the corresponding values for adults. The data suggest that transfer of PCB's via the milk is much more significant than placental transfer. There appears to be a placental barrier against PCB's. (16 refs)

79-1410 Influence of Genetic Population Structure on the Results of Chronic Toxicity Studies. (Eng)

Littlefield, N. A. (Natl. Center Toxicological Res., Jefferson, AR, 72079); Kodell, R. L. *J Toxicol Environ Health* 5(1): 121-129; 1979.

Offspring from a BALB/cStCrIFC3Hf/Nctr male and C567BL/6JfC3Hf/Nctr female cross were used to produce a homogeneous (F₁) strain, and brother-sister mating of the F₁ population was used to produce a heterogeneous (F₂) strain of mice, both having essentially the same gene pool but with different distributions. These mice were exposed over their life-span to benzidine dihydrochloride (0-160 ppm in the drinking water) in an experiment to provide data demonstrating the relative variability about the mean of response to a carcinogen in genetically homogeneous and heterogeneous groups of mice. There were four groups of mice divided by sex and by F₁ and F₂ population, and each group totaled 648 mice; 72 mice were used for each dose level within each group. All dose levels were toxic, as indicated by body wt loss. F₁ mice were significantly heavier and had a lower mortality rate than the F₂ animals. There were 82 animals left after termination of the study at 33 mo, 66 controls and 16 treated mice; 59 were F₁ and 23 were F₂. These ratios are consistent with the data showing that F₂ mice are more sensitive and have shorter life-spans than F₁ mice. Thus, the genetic constitution of research animals should be an important consideration in toxicological investigations. Although the same alleles existed in these two populations, their distribution, identical in F₁ and randomly distributed in F₂, resulted in significant differences between the two populations in body wt and mortality. (9 refs)

79-1411 Characterization of Chronic N,N'-F1-Diacetylbenzidine-induced Nephropathy. (Eng)

Zimmerman, S. W. (Dept. Medicine, Univ. Wisconsin Center

Health Sciences, Madison, WI, 53706). *Am J Pathol* 94(2): 285-300; 1979.

Glomerular (GM) lesions induced in female Sprague-Dawley rats by chronic N,N'-diacetylbenzidine (DAB) administration were characterized with regard to amount of proliferation and "crescent" formation and their relationship to urinary protein excretion. The rats received weekly ip injections of 0.1-0.25 ml of a suspension of 1 g DAB in 10 ml ethanol for up to 20 wk. Some of the rats underwent left nephrectomy (Nx) prior to treatment. Animals were killed 1.5-35 wk after receiving 45-230 mg DAB. Those with the most significant GM lesions had significant proteinuria (PU). DAB dose did not appear to relate to histologic alterations--several rats received 75-180 mg DAB but failed to demonstrate dramatic histologic alterations or significant PU. Significant PU occurred at ± 10 wk, and it was enhanced by prior unilateral Nx. GM epithelial cell vacuolization and cyst formation were marked in proteinuric rats. Focal GM sclerosis and synechia were present, but proliferative crescent formation was not. GM fibrinogen was noted, but no immunoglobulins or complement was detected by immunofluorescence microscopy. GM epithelial cell cysts and disruption were seen ultrastructurally, but there were no electron-dense deposits. Tubular basement membranes were focally thickened and wrinkled, and max urine osmolality was decreased. None of the animals developed renal insufficiency. Parenteral DAB-induced renal disease is different from the crescentic glomerulonephritis noted in rats fed DAB, and it has similarities to an experimental model of aminonucleoside-induced focal sclerosis, supporting the theory of primary GM epithelial cell injury mediating PU and focal sclerosis. (20 refs)

79-1412 Azathioprine-induced Lymphocytic Neoplasms of NZB Mice Lack Ecotropic Murine Leukemia Virus. (Eng) Harvey, J. J. (MRC Clinical Res. Centre, Harrow, Middlesex, England); East, J.; Katz, F. E. *Int J Cancer* 23(2): 217-223; 1979.

The concept that the presence of an ecotropic viral genome is an essential cocarcinogenic factor for the induction of lymphocytic (LC) malignancy was investigated in New Zealand Black (NZB) mice, in which LC neoplasms were induced by long-term treatment with the immunosuppressant azathioprine (ATP: Imuran). Im injection of 2.5 mg/25 g ATP 3x/wk for 4 wk, 2x/wk during wk 5, and 1x/wk for up to 6 mo resulted in LC lymphomas 6-7 mo after the start of treatment. These malignancies were distinct from the reticulum cell tumors that occur spontaneously in this strain, and they were readily transplantable to NZB or histocompatible BALB/c recipients. In addition, leukemic cells stored in liquid nitrogen for 6 yr proliferated rapidly when injected into newborn syngeneic mice. Virus filtrates prepared from donor leukemic tissues were nonpathogenic when injected into newborn C3H mice. Xenotropic, but not ecotropic, murine leukemia virus was detected in leukemic tissues of some donor and recipient NZB mice when tested in vitro by cocultivation with permissive cell lines, genome rescue, and by XC and

viral polymerase assays. These findings indicate a need to reassess the concept that LC malignancies and, perhaps, other types of malignancies induced by methods other than deliberate virus infection are necessarily due to activation of an ecotropic viral genome. (48 refs)

79-1413 Effect of Mutagens, Chemotherapeutic Agents and Defects in DNA Repair Genes on Recombination in F' Partial Diploid *Escherichia coli*. (Eng) Norin, A. J. (Montefiore Hosp. and Medical Center, Albert Einstein Coll. Medicine, C-416, 111 E. 210th St., Bronx, NY, 10467); Goldschmidt, E. P. *Mutat Res* 59(1): 15-26; 1979.

The effects of mutagens, chemotherapeutic agents that inhibit DNA synthesis, a DNA polymerase I mutation, and a UV excision-repair mutation on recombination in F' partial diploid (F30) *Escherichia coli* were compared. The assay involved determining the proportion of His⁺ homogenote recombinants that arose from a His⁺ heterogenote. The mutagens increased the percentage of haploid and auxotrophic colonies, but Hfr recombinants were not observed. At least 75% of the recombinants were homozygous for histidine alleles that were present on the F' plasmid (exogenote) of the parental heterogenote rather than for histidine alleles on the chromosome. Mutagens, agents that inhibit DNA synthesis (2-aminopurine and methotrexate), and a defective DNA polymerase I gene (*polA1*) increased the frequency of non-reciprocal recombination. A defect in the ability to excise thymine dimers, *uvrC34*, did not increase spontaneous non-reciprocal recombination. However, UV irradiation but not methyl methanesulfonate (MMS) induced greater recombination in this excision-repair-defective mutant than in DNA-repair-proficient strains. Mutagenic agents, with the exception of ethyl methanesulfonate (EMS), induced greater increases in recombination than the DNA synthesis inhibitors or the *polA1* mutation. EMS was more mutagenic but less recombinogenic than MMS. One explanation for these results is that DNA synthesis inhibition increases recombination by prolonging the lifetime of naturally occurring single-stranded regions in replicative intermediates of the DNA. Mutagens that cause the rapid breakdown of DNA may, in addition, introduce lesions into the genome that increase the number of single-stranded regions, thus inducing even higher frequencies of recombination. (37 refs)

79-1414 Transport and Metabolism of Methotrexate in Normal and Resistant Cultured Rat Hepatoma Cells. (Eng) Galivan, J. (Div. Labs. and Res., New York State Dept. Health, Albany, NY, 12201). *Cancer Res* 39(3): 735-743; 1979.

The transport and metabolism of the antifolate drug methotrexate (MTX) were examined in monolayer cultures of a continuous cell line derived from the Reuber H35 hepatoma. The H35 cells had a doubling time of approx 19 hr and could not grow in the presence of 3×10^{-6} M MTX. The cells exhibited a linear uptake of MTX that lasted for 4-6 hr and reached

a steady state after approx 16 hr. The uptake was saturable, with a max rate of 1.1 nanomoles/min/g cell protein at $\geq 18 \mu\text{M}$ MTX. 5-Methyltetrahydrofolate markedly inhibited uptake at an equimolar concentration, but folic acid exerted no effect at a five-fold excess. Once inside the cell, MTX was rapidly converted to its polyglutamate derivatives with a conversion $> 90\%$ when the intracellular concentration was $> 2 \mu\text{M}$. Resistant sublines were developed by culturing H35 cells in increasing concentrations of MTX. These cells were similar to the parent cells in levels of dihydrofolate reductase, thymidylate synthetase, and the extent that MTX could be converted to its polyglutamate derivatives. They appeared to differ from normal cells in not having the capacity for the extended linear uptake that is observed with normal cells. As a result, there was a greatly reduced concentration of MTX and its polyglutamates at steady state. These results suggest that the cells become resistant as a result of a stable change in the transport system for MTX, but the mechanism of this process is not yet understood. (61 refs)

- 79-1415 Transplacental Effects of Chemical Mutagens Detected by the Micronucleus Test.** (Eng) Cole, R. J. (Developmental Genetics Group, Sch. Biological Sciences, Univ. Sussex, Falmer, Brighton, England); Taylor, N. A.; Cole, J.; Arlett, C. F. *Nature* 277(5694): 317-318; 1979.

Chromosome damage in fetal mouse tissue following transplacental exposure to chemicals that require metabolic activation was studied. A kinetic model was constructed that predicted that the transplacental and maternal effects of chromosome-damaging agents could be compared by measuring the incidence of polychromatic RBC containing micronuclei 12-30 hr after exposure. If each of the target cells received damage leading to formation of a single micronucleus, the max incidence of polychromatic RBC containing micronuclei in fetal liver and bone marrow would be about 25%. The frequency of polychromatic RBC in the blood was predicted to be about 60% of the peak in the fetal liver. Pregnant Swiss albino mice were inoculated ip with mitomycin C (2 mg/kg) or procarbazine hydrochloride (10-100 mg/kg). With both agents, damage to the fetal liver was greater than that to the adult bone marrow. After mitomycin C, the spontaneous incidence of micronucleated RBC was 0.16% in the adult bone marrow, 0.4% in the fetal liver, and 0.24% in the fetal blood. These results establish the usefulness of the RBC micronucleus test applied to prenatal mice. (12 refs)

- 79-1416 Isolation of Polyaromatic Hydrocarbons from Whole Smoke Condensate: A Simple Two-Step Procedure.** (Eng) Levins, R. J. (Res. Center, P.O. Box 26583, Richmond, VA, 23261); *Chromatographia* 11(12): 736-741; 1978.

A rapid, simple, two-step procedure for the isolation of polyaromatic hydrocarbons (PAHs) from whole smoke con-

densate (WSC) is described. A crude PAH fraction is isolated by preparative thin-layer chromatography, and is then further enriched by gel permeation chromatography on Sephadex LH-20. A complete analysis, including a gas chromatographic temperature-programmed profile of the PAH fraction, can be performed in less than 8 hr, permitting the comparison of the gas chromatographic scans of the PAH fractions from a number of WSCs in a relatively short time. (13 refs)

- 79-1417 Level of Pesticide Residues in Beer.** (Fre) Gouraud, J. (Ecole nationale superieure des industries agricoles, 59509 Douai, France); Scriban, R. *Ann Nutr Aliment* 32(5): 975-979; 1978.

A method is presented for the extraction, purification, and gas chromatographic analysis of several pesticides, including dieldrin and 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), in beer. (2 refs)

- 79-1418 Metabolism of 7,12-Dimethylbenz[a]anthracene and Its Methylhydroxylated Derivatives: Formation of Phenolic Metabolites at the 2-Positions (Meeting Abstract).** (Eng) Yang, S. K. (Uniformed Services Univ. Health Science, Bethesda, MD, 20014); Chou, M. W. *Fed Proc* 38(3, Part 1): 425; 1979. (no refs)

- 79-1419 Metabolism of DMBA by Rat Pancreas In Vivo and In Vitro (Meeting Abstract).** (Eng) Black, O. (Medical Coll. Georgia, Augusta, GA, 30904). *Fed Proc* 38(3, Part 1): 426; 1979. (no refs)

- 79-1420 A Quantitative Determination of the Covalent Binding of a Series of Polycyclic Hydrocarbons to DNA in Mouse Skin.** (Eng) Phillips, D. H. (McArdle Lab. Cancer Res., Univ. Wisconsin Medical Center, Madison, WI, 53706); Grover, P. L.; Sims, P. *Int J Cancer* 23(2): 201-208; 1979.

The binding of seven ^3H -labeled polycyclic hydrocarbons to DNA in C57BL mouse skin following topical application was studied. DNA isolated from the treated areas was hydrolyzed enzymically to deoxyribonucleosides, and the products were chromatographed on Sephadex LH20 columns. The levels of binding of hydrocarbon to DNA were determined from the amounts of radioactivity eluted from Sephadex LH20 columns in those fractions containing hydrocarbon-DNA adducts. Tritium incorporation into normal deoxyribonucleosides was examined by rechromatography of material on AG50W-X4 columns and in some instances it was found to account for a substantial proportion of the total radioactivity associated with DNA samples. Following treatment of mice with 1 micromole of hydrocarbon/mouse, 7,12-dimethylbenz(a)anthracene, the most potent carcinogen studied, became bound to DNA to the greatest extent [43 picomoles

(pmol)/mg DNA] Benzo(a)pyrene and 3-methylcholanthrene, the next most active compounds, became bound to DNA to similar extents (27 and 25 pmol/mg DNA), as did 7-methylbenz(a)anthracene (25 pmol/mg DNA), although it is a less active compound. Dibenz(a,h)anthracene, another moderately active hydrocarbon, became bound to DNA to the extent of 15 pmol/mg DNA, and the very weakly active compounds benz(a)anthracene (2 pmol/mg DNA) and dibenz(a,c)anthracene (10 pmol/mg DNA) became bound to DNA to the lowest extents. Dibenz(a,h)anthracene differed from the other hydrocarbons in showing a max level of binding 72 hr after treatment, compared with 19-24 hr for the other compounds. (33 refs)

- 79-1421 Role of Acid-Base Balance in Tumor Manifestation: An Experimental Study in Two-Stage Skin Carcinogenesis.** (Eng) Stenback, F. (Dept. Pathology, Univ. Oulu, Oulu, Finland); Ryan, W.; Curtis, G. *IRCS Med Sci (Cancer)* 7(1): 45; 1979.

A study of the effect of prolonged metabolic alkalosis or acidosis on the induction of skin tumors in female Swiss mice by 7,12-dimethylbenz(a)anthracene + phorbolmyristate acetate demonstrated a significant increase in the number of tumors and tumor-bearing animals associated with alterations in the acid-base balance. Although both bicarbonate-induced alkalosis and ammonium chloride-induced acidosis increased tumorigenesis, the effect was more pronounced with the former. (2 refs)

- 79-1422 Influence of Dietary Fat on Microsomal Monooxygenases: Possible Relationship to 7,12-Dimethylbenzanthracene (DMBA)-induced Mammary Cancer (Meeting Abstract).** (Eng) Rikans, L. E. (Dept. Pharmacology, Univ. Oklahoma Health Science Center, Oklahoma City, OK, 73104); Gibson, D. D.; McCay, P. B. *Fed Proc* 38(3, Part 1): 365; 1979. (1 ref)

- 79-1423 Effect of Reserpine on the Incidence of 9,10-Dimethyl-1,2-benzanthracene-induced Tumors in Pinealectomized and Thymectomized Rats.** (Ger) Lapin, V. (Institut für Krebsforschung, Universität Wien, Borschkegasse 8a, A-1090 Vienna IX, Austria). *Onkologie* 1(1): 2-5; 1978.

The effects of neonatal pinealectomy (Pi-x) and/or thymectomy (Th-x) and reserpine (RP) treatment on tumor induction by 9,10-dimethyl-1,2-benzanthracene (DMBA) were studied in male and female Wistar rats. Group 1 received DMBA (3 doses of 50 mg/kg via gastric intubation at 10-day intervals) and then RP (100 µg/kg/day sc for 40 days) starting 1 mo after the first DMBA dose. Group 2 received DMBA and then physiological saline soln instead of RP. Group 3 received RP only. In Group 1, tumor incidence was 12/19 in nonoperated rats, 15/15 in Pi-x rats, 10/15 in Th-x rats, and 6/6 in Pi-x + Thy-x rats. In Group 2, tumor incidence was

5/12 in nonoperated animals, 5/12 in Pi-x rats, 7/16 in Th-x rats, and 4/6 in Pi-x + Th-x rats. In Group 3, no tumors were found in the four subgroups. Among the DMBA-treated animals, survival was shortest in the Pi-x group (239 days vs 310-319 days in Th-x and intact animals). Hormone-dependent tumors of the breast and auditory meatus were most frequent. Nephroblastoma was found in two Th-x rats. Leukemia was seen sporadically in the DMBA-treated animals (incidence, 6.74%); however, leukemia does not occur spontaneously in these rats. Leukemia incidence was highest in the Pi-x rats in Group 1. The findings indicate that the carcinogenic effect of DMBA is not enhanced substantially by neonatal Pi-x and that neonatal Th-x does not increase the susceptibility of rats to the carcinogenic effect of DMBA. Although RP alone had no harmful or carcinogenic effect, it increased the incidence of DMBA-induced tumors in Pi-x rats. (14 refs)

- 79-1424 In Vivo and In Vitro Studies of Experimental Ovarian Adenocarcinoma in Rats.** (Eng) Sekiya, S. (Dept. Obstetrics and Gynecology, Chiba Univ. Sch. Medicine, Inohana 1-8-1, Chiba 280, Japan); Endoh, N.; Kikuchi, Y.; Katoh, T.; Matsuura, A.; Iwasawa, H.; Takeda, B.; Takamizawa, H. *Cancer Res* 39(3): 1108-1112; 1979.

The induction of adenocarcinoma-type ovarian tumors in female Sprague-Dawley rats by the "clipping" method using the carcinogens 7,12-dimethylbenz(a)anthracene (DMBA) and 20-methylcholanthrene (20-MC) is described, along with the establishment of two cloned cell lines from these tumors in vitro. Silk sutures were soaked in a melted mixture of carcinogen:beeswax (1:3) and allowed to dry, and they were then inserted into the right side of the ovarian parenchyma by a surgical needle through a single middorsal incision and knotted. The av amount of carcinogen per suture was 1.92 mg. Tumor development was checked by weekly palpation over a 50-wk period. Tumors occurred in 36/75 DMBA-treated rats, and 29/36 tumors were adenocarcinomas. Tumors occurred in 6/31 20-MC-treated rats, but only 1/6 tumors was an adenocarcinoma. In attempts to culture adenocarcinoma tissue specimens, initial growth was found to be strongly influenced by the specific lactate dehydrogenase activity of the tumor tissues. The mean specific activity of the successful cases was 1,020 units/g protein, vs 365 units for the failures. Two cloned cell lines were isolated, both of which were epithelioid. When approx 1.5×10^6 cells of these lines were injected sc into isologous newborn rats, tumors developed after 6 wk in 5/6 and 3/7 rats, respectively. The tumors were undifferentiated adenocarcinomas. (13 refs)

- 79-1425 Compartment Model of Carcinogenic Promoter Activity.** (Eng) Lipetz, P. D. (Ohio State Univ., Columbus, Ohio, 43210). *Diss Abstr Int B* 39(8): 3661; 1979. (no refs)

- 79-1426 Quantitative Correlation between In Vitro and In Vivo Activities of Phorbol Esters.** (Eng)

Driedger, P. E. (Dept. Pharmacology, Harvard Medical Sch., Boston, MA, 02115); Blumberg, P. M. *Cancer Res* 39(3): 714-719; 1979.

The effects of various phorbol derivatives on surface large external transformation-sensitive glycoprotein (LETSP) levels and on deoxyglucose (DG) transport in normal chicken embryo fibroblasts were determined. Dose-response data indicated that with one exception [phorbol 12,13-dibenzoate (PDB)], these derivatives all caused a comparable max decrease in LETSP, whereas their half-maximally effective doses (ED_{50} 's) varied over a range of four orders of magnitude. Good quantitative correlation was obtained between these ED_{50} 's and the inflammatory potencies (quantity causing ear inflammation in 50% of a group of treated mice, ID_{50} 's) of these derivatives in the mouse ear assay. With respect to stimulation of DG transport, the phorbol esters fell into two categories. Phorbol 12-myristate-13-acetate (PMA), phorbol 12,13-diacetate, and phorbol 12,13,20-triacetate showed ED_{50} 's for stimulating DG transport that closely matched their ED_{50} 's for causing loss of LETSP (and thus their ID_{50} 's in the mouse ear assay). Phorbol 12,13-didecanoate, PDB, and 4-O-methylphorbol 12-myristate-13-acetate were four- to ninefold more potent in stimulating DG transport than in causing LETSP loss. Unlike the phorbol esters, the parent diterpene phorbol and free myristic acid had little effect on DG transport or LETSP levels at concentrations up to 3 and 0.2 millimolar, respectively, above which toxicity was observed. For PMA, the relation between stimulation of DG transport and toxicity was examined. In contrast to a 3.7 nanomolar ED_{50} for stimulation by PMA, inhibition of this stimulation occurred only with an ED_{50} of 3.3 μ M and cell lysis occurred with an ED_{50} of 11 μ M. (51 refs)

79-1427 Modulation of Plasminogen Activator Expression by Tumor Promoting Phorbol Esters. (Eng)

Wigler, M. H. (Columbia Univ., New York, NY). *Diss Abstr Int B* 39(8): 3653-3654; 1979. (1 ref)

79-1428 Plasma Membrane Alterations in Phorbol Myristate Acetate (PMA)-Treated Myogenic Cells (Meeting Abstract). (Eng) Schimmel, S. D. (Dept. Biochemistry, Coll. Medicine, Univ. South Florida, Tampa, FL, 33612); Hallam, T.; Grotendorst, G.; Breiner, J.; Grove, R. I. *Fed Proc* 38(3, Part 1): 665; 1979. (1 ref)

79-1429 Tumor Promoter 12-O-Tetradecanoylphorbol-13-acetate Is Not a Prostaglandin E-Type Agonist. (Eng) Furstenberger, G. (Inst. Biochemistry, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany); Marks, F. *Cancer Lett* 6(2): 73-77; 1979.

The ability of the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) to compete with E-type prostaglandins (PGE) for an established PGE receptor was tested in a com-

petition binding assay using lipocytes prepared from male Wistar rats. In doses up to a 400-molar excess (1,230 nanograms 2×10^{-4} M), TPA could not significantly displace PGE_1 from its receptor in the fat cell membrane. Similar observations were made using receptor preparations from adipose tissue instead of intact fat cells. Under the conditions used, TPA was not chemically altered. These results provide evidence that TPA is not a PGE agonist, at least as far as the PGE_1 receptor of fat cells is concerned. (10 refs)

79-1430 Tumor Development in Organ Transplants Obtained from Carcinogen-exposed Rats. (Eng)

Yarita, T. (Dept. Surgery, Inst. Pulmonary Cancer Res., Sch. Medicine, Chiba Univ., Chiba 280, Japan); Nettesheim, P. *J Natl Cancer Inst* 62(2): 417-424; 1979.

To determine whether carcinogenesis initiated by N-nitrosoheptamethyleneimine (NHMI) in prospective tissue donors is affected by transplantation of target organs by grafting onto isogenic recipients, tumor development in situ and in transplanted tracheas and esophagi was followed 70-80 wk in male F344 rats. Rats were given 15 mg NHMI/kg by intragastric intubation 3x/wk for 5 wk (for a total of 225 mg/kg) or 10 wk (for a total of 450 mg/kg). Carcinogenesis was not disrupted by the transplantation procedure. A dose-response relationship was seen in both systems, and the histopathologic changes developing as a function of time appeared to be similar in transplanted and in situ tracheas and esophagi. The proportion of carcinomas to papillomas in transplanted esophagi was markedly higher however, and the tracheal tumor response gave indications of the same trend. At high carcinogen dose, tumor incidence was 100% in transplanted esophagi and 90% in situ, while tracheal incidence was 20% and 25% in situ and in transplants, respectively. At low dose, only one tracheal tumor developed (in a transplanted organ), and the esophagus tumor incidence was 36% in situ and 100% in transplants. These results indicate that tumor response in heterotropic transplants is enhanced as compared with in situ tumor development. (19 refs)

79-1431 Effect of Alkane Tumor-promoting Agents on Chemically Induced Mutagenesis in Cultured V79 Chinese Hamster Cells. (Eng) Lankas, G. R. (Dept. Environmental Health, Univ. Cincinnati Medical Sch., Cincinnati, OH, 45267); Baxter, C. S.; Christian, R. T. *J Toxicol Environ Health* 4(1): 37-41; 1978.

Linear alkanes with even chain lengths of 6-14 carbon atoms, 1-phenyldodecane (PDD), and 12-O-tetradecanoylphorbol-13-acetate (TPA) were tested in ouabain-resistant mutant V79 Chinese hamster cells for their ability to enhance mutagenesis induced by methylazoxymethanol acetate (MAM). The cells were incubated with MAM (24 μ g/ml) for 24 hr, after which the medium was replaced by fresh medium containing the chemical being tested for promoting activity. n-Hexane, n-decane, n-dodecane, n-tetradecane, and n-hexadecane were tested at 0.12 mM, PDD at 0.7 mM, and TPA

at 1.6 μ M. At these concentrations, none of the alkanes was toxic and MAM-induced toxicity was not affected. No alkane was mutagenic by itself. Enhancement of MAM-induced mutation frequency was observed with n-decane, n-dodecane, and n-tetradecane, but not with n-hexane or n-hexadecane. These results are in good agreement with the relative promoting activities of these agents in mouse skin. TPA and PDD enhanced MAM-induced mutagenesis to a similar degree, indicating that on a molecular basis TPA is approx 400 times more potent than PDD in this system. These results suggest a critical role for mutagenesis in the initiation of carcinogenesis and support the theory that promoters act by inducing changes at the level of the genome, causing expression of latent damage associated with carcinogen-induced mutations. (9 refs)

- 79-1432 5,6-Epoxyretinoic Acid Opposes the Effects of 12-O-Tetradecanoylphorbol-13-acetate in Bovine Lymphocytes.** (Eng) Wertz, P. W. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706); Kensler, T. W.; Mueller, G. C.; Verma, A. K.; Boutwell, R. K. *Nature* 277(5693): 227-229; 1979.

The synthesis and testing of 5,6-epoxyretinoic acid as an antagonist of the effects of the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) in bovine lymphocytes are reported. For comparison, tests were also conducted with retinoic acid. 5,6-Epoxyretinoic acid inhibited the TPA-accelerated incorporation of choline into the phospholipids of bovine lymphocytes more effectively than did retinoic acid. It was also a more effective inhibitor of ornithine decarboxylase induction by TPA in bovine lymphocytes. Thus, introduction of an epoxide group at the 5,6-position of retinoic acid results in an enhanced ability to oppose certain effects of TPA in bovine lymphocytes. These results do not prove the concept of metabolic activation of retinoic acid, but they are consistent with the suggestion that an activation process may involve epoxidation at the 5,6-position. These results also demonstrate that bovine lymphocytes are a good indicator system for studying the modulation of metabolic processes by phorbol esters and retinoids. (16 refs)

- 79-1433 The Effects of Fatty Acids and Antioxidants in the Culture Medium on Membrane Composition and Properties of the Microsomal Enzymes Aryl Hydrocarbon Hydroxylase and Cytochrome c Reductase of Cultured Liver Cells.** (Eng) Chenery, R. J. (Lab. Toxicology and Pharmacokinetics, Dept. Clinical Pharmacology, Univ. Coll. Hosp. Medical Sch., University St., London WC1E 6JJ, England); McLean, A. E. *Biochim Biophys Acta* 572(1): 9-18; 1979.

The possibility of a role for fatty acids in the control of aryl hydrocarbon hydroxylase (AHH) activity in cell culture was examined using rat liver epithelial cells. Cells grown in medium without serum showed characteristic changes in fatty acid composition and decreased levels of AHH activity. Cell fatty

acid composition was manipulated using albumin-fatty acid complexes. Both gas-liquid chromatographic analysis of fatty acid methyl esters and Arrhenius plots of enzyme activity indicated changes in membrane lipid composition without major changes in AHH activity or inducibility by 1,2-benzanthracene in the presence of the antioxidant butylated hydroxytoluene. The effects of adding palmitate, oleate, linoleate, and arachidonate to the culture medium were also investigated. The saturated and monounsaturated fatty acids were ineffective at altering either basal or induced levels of AHH. In the absence of the antioxidant, both linoleic acid and arachidonic acid caused significant enhancement of AHH activity. Substantial cytotoxic effects were also observed under these conditions. The changes in microsomal AHH activity were independent of changes in cytochrome c reductase. It is concluded that AHH activity in cell culture is not directly related to cell fatty acid composition, but induction by 1,2-benzanthracene can occur with only minute concentrations of essential fatty acids present in the cellular lipids. (34 refs)

- 79-1434 An Appraisal of Relative Airborne Sub-Urban Concentrations of Polycyclic Aromatic Hydrocarbons Monitored Indoors and Outdoors.** (Eng) Butler, J. D. (Dept. Chemistry, Univ. Aston, Birmingham, B4 7ET, England); Crossley, P. *Sci Total Environ* 11(1): 53-58; 1979.

Particle-size distribution and concentration studies of airborne polycyclic aromatic hydrocarbons were conducted at three indoor and three outdoor sites in and around the city of Birmingham, England. The mass median equivalent diameter of total particulate matter was approx 1 μ M at all outdoor sites. At all sites, chrysene concentrations were the highest at 4-7 nanograms (ng)/m³, followed by benzo(a)pyrene and benzo(e)pyrene at 2-4 ng/m³, with coronene less than 1 ng/m³. (9 refs)

- 79-1435 The Effects of Chronic Emetine Treatment on Protein Synthesis (Meeting Abstract).** (Eng) Dubick, M. A. (Dept. Pharmacy, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033); Yang, W. C. *Fed Proc* 38(3, part 1): 537; 1979. (no refs)

- 79-1436 Ecogenetics.** (Ger) Goedde, H. W. (Institut für Humangenetik, Universität Hamburg, Butenfeld 32, D-2000 Hamburg 54, W. Germany). *Fortschr* 97(4): 127-128, 165-167; 1979.

Persons with high inducibility of aryl hydrocarbon hydroxylases (AHH) by certain carcinogens, such as benzantracene, methylcholanthrene, and hexobarbital, are considered to be especially likely to develop lung cancer. A comparative study of 50 lung carcinoma patients and 85 tumor-free controls revealed that the incidence of high AHH inducibility was 30% in the cancer patients vs 9.4% in the controls. The incidence of medium inducibility was 66% in the patients and

45.9% in the controls, whereas that of low inducibility was 4% in the patients and 44.7% in the controls. (8 refs)

- 79-1437** Effects of Subcutaneous Administration of 3-Methylcholanthrene and 7,12-Dimethylbenz(a)anthracene on Spontaneous Reticulum Cell Neoplasms in SJL/J Mice. (Eng) Whitmire, C. E. (Toxicology Branch, Carcinogenesis Testing Program, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD, 20014). *J Natl Cancer Inst* 62(3): 561-564; 1979.

The interaction of the spontaneous reticulum cell neoplasms (RCN's) associated with SJL/J inbred mice and sc carcinogenesis induced by 3-methylcholanthrene (3-MC) and 7,12-dimethylbenz(a)anthracene (DMBA) was determined. Inbred 4- and 16-wk-old SJL/J mice were treated sc with either 150 or 450 µg 3-MC. No difference was noted in their sc tumor response related to age. Although the incidences of RCN's were the same in the controls for the two age groups, more 16-wk-old animals developed RCN's after carcinogen treatment than did 4-wk-old SJL/J mice. More 16-wk-old mice developed both sc tumors at the site of 3-MC injection and systemic RCN's than did mice treated at 4 wk of age. This incidence was related to the coincidence of the chronological age of the mice for RCN development with the latency for chemical carcinogen-induced sc tumor development. Mice treated with DMBA at 16 wk of age responded in the same way as did those treated with 3-MC. (7 refs)

- 79-1438** Simultaneous Determination of Cellular Mutagenesis and Transformation by Chemical Carcinogens in Fischer Rat Embryo Cells. (Eng) Mishra, N. K. (Microbiological Associates, 5221 River Road, Bethesda, MD, 20016); Wilson, C. M.; Pant, K. J.; Thomas, F. O. *J Toxicol Environ Health* 4(1): 79-91; 1978.

An assay was developed for simultaneous measurement of transformation and induced mutation (ouabain resistance) in Fischer rat embryo (FRE) cells infected with Rauscher leukemia virus (RLV). Virus-positive cells were subcultured 7 days after infection and fed 48 hr later with medium containing the test chemical (day 0). The cells were refed with chemical-containing medium on day 5; the chemical was removed on day 7, and the cultures were passaged serially for 10-12 subcultures. Cells at the third subculture were tested for ouabain resistance. For the transformation assay, the cells were monitored at each subculture for morphological alteration and growth in soft agar. The assay was validated in tests using eight carcinogens [3-methylcholanthrene, dimethylbenz(a)anthracene, benzo(a)pyrene, N-methyl-N'-nitro-N-nitrosoguanidine, 4-nitroquinoline-N-oxide, methylazoxymethanol acetate, N-2-fluorenylacetylacetamide (AAF), and dimethylnitrosamine (DMN)] and five noncarcinogens. All chemicals known to be carcinogenic in rodent bioassays except DMN and AAF induced transformation or mutation. DMN but not AAF could be activated by the addition of rat liver homogenates. All chemicals that produced transforma-

tion also induced a significant increase in ouabain resistance. It is concluded that the simultaneous measurement of drug resistance and transformation is effective for routine screening. (21 refs)

- 79-1439** Growth Retardation in Post-Partum Pups due to Dimethylbenzanthracene (DMBA) Administration in Pregnant Rats. (Eng) Pitkow, H. S. (Dept. Physiological Sciences, Pennsylvania Coll. Podiatric Medicine, Philadelphia, PA, 19107); Citron, A.; Rizen, H.; Davis, R. H. *Pro Pennsylvania Acad Sci* 52(1): 34-36; 1978.

The effect of the carcinogen 7,12-dimethylbenzanthracene (DMBA: 1 mg/day ip during days 8 through 12 of pregnancy) on the neonatal development and maternal organ wts of Long Evans rats was studied. DMBA significantly increased the gestation period from 19.3 to 23.9 days. It decreased the wts of pups weighed on days 6, 11, 17, and 28 after birth, the decrease being significant in the case of the 6- and 28-day-old pups. DMBA also significantly decreased the dry mammary gland wt and heart wt of the dams, but had no significant effects on mammary milk content or liver and kidney wts of the dam. The data indicate that DMBA may have a deleterious effect on the maternal cardiovascular system and that it has an in utero inhibiting effect on the future growth of pups. (8 refs)

- 79-1440** Structural Gene Products of the Murine Ah Locus: Immunochemical Evidence for Two Forms of Liver P-450 Induced by 3-Methylcholanthrene (Meeting Abstract). (Eng) Negishi, M. (NICHD, NIH, Bethesda, MD, 20014); Nebert, D. W. *Fed Proc* 38(3, Part 1): 495; 1979. (no refs)

- 79-1441** The Effect of Two Polychlorinated Biphenyls (Kanechlor 500 and Delor 106) and 3-Methylcholanthrene on the Activity of Some Rat Liver Microsomal Enzymes. (Ger) Butschak, G. (Zentralinstitut für Krebsforschung, Akademie der Wissenschaften, DDR, 1115 Berlin-Buch, E. Germany); Teichmann, B.; Scheunig, G.; Ziebarth, D. *Acta Biol Med Ger* 37(7): 969-977; 1978.

The effects of Kanechlor 500 (500 mg/kg ip), Delor 106 (500 mg/kg ip), and 3-methylcholanthrene (3-MC; 100 mg/kg ip), injected in single doses into 4 to 5-wk-old male Wistar rats, on the enzymatic demethylation of ethylmorphine (EM), dimethylnitrosamine (DMNA), and 4-dimethylaminoazobenzene (DAB) and on the activity of aryl hydrocarbon hydroxylase (AHH) with benzo(a)pyrene as substrate and of azoreductase with DAB as substrate were studied. 3-MC had no effect on the demethylation of EM, and it caused a considerable but insignificant increase in the demethylation of DMNA. However, 3-MC significantly increased the demethylation of DAB by a factor of 2.5. All three demethylation reactions were increased significantly by both polychlorinat-

ed biphenyls (PCB's): Delor 106 caused an increase by a factor of 3-6, and its effect was 20%-30% higher than that of Kanechlor 500. AHH and azoreductase activities were increased by all three inducers more than fourfold compared with the initial activities. The PCB's, especially Delor 106, were more active than 3-MC. The findings indicate that PCB's are suitable for the pretreatment of experimental animals from which enzyme preparations are to be used in the mutagenicity screening of potential carcinogens. (41 refs)

79-1442 Effects of Subcutaneous Administration of Chemical Carcinogens on Leukemia in C58 Mice. (Eng) Whitmire, C. E. (Toxicology Branch, Carcinogenesis Testing Program, Div. Cancer Cause and Prevention NCI, NIH, Bethesda, MD, 20014). *J Natl Cancer Inst* 62(3): 555-559; 1979.

The effects of sc administration of 3-methylcholanthrene (3-MC: 150 or 300 μ g), 7,12-dimethylbenz(a)anthracene (DMBA: 150 or 300 μ g), and benzo(a)pyrene (BP: 150 μ g) on spontaneous viral leukemia and sc sarcoma induction were evaluated in weanling C58/J mice. 3-MC produced significantly more sarcomas at the inoculation site than did DMBA or BP; moreover, it interfered with leukemia development (the incidence was 0% and 5% at 150 and 300 μ g, respectively, vs 33% in controls). DMBA produced fewer sarcomas, and the incidence of leukemia was comparable to that found in controls. BP accelerated the incidence of leukemia (to 52%), although no sarcomas were produced. When the effect of the age of the mice at the time of 3-MC treatment on the incidence of leukemia and sarcomas was studied, newborn and weanling mice were found to develop primarily sarcomas. In contrast, no sarcomas were produced in 16-wk-old mice, and 52%-64% developed leukemia. The reason no sarcomas were found in the C58 mice was apparently different from the reason no sarcomas were found in AKR mice, inasmuch as the AKR mice did not live long enough for sarcomas to develop. Immunologic surveillance may have played a part in the sarcoma suppression in the C58 mouse. (16 refs)

79-1443 Aryl Hydrocarbon Hydroxylase Activity in the Adrenal Gland of the Rat and Mouse: Effect of 3-Methylcholanthrene Treatment (Meeting Abstract). (Eng) Menard, R. H. (NIH, Bethesda, MD, 20014); West, D. M.; Mattison, D. R.; Gelboin, H. V. *Fed Proc* 38(3, part 1): 527; 1979. (no refs)

79-1444 Comparative Induction of Intestinal Mixed-Function Oxidase Activities by Various Polycyclic Hydrocarbons (Meeting Abstract). (Eng) Hassing, J. M. (Univ. Nebraska Medical Center, Omaha, NE, 68105); Stohs, S. J. *Fed Proc* 38(3, part 1): 365; 1979. (no refs)

79-1445 Determination of Benzo(a)pyrene and Other Polynuclear Aromatic Hydrocarbons in Air-

borne Particulate Material by Ultrasonic Extraction and Reverse Phase High Pressure Liquid Chromatography. (Eng) Golden, C. (Environmental Sciences Res. Lab., Office Res. and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC, 27711); Sawicki, E. *Anal Lett* 11(12): 1051-1062; 1978.

A procedure for determining benzo(a)pyrene (BP) and other polynuclear aromatic hydrocarbons (PAH) in airborne particulates is described. The method consists of improved ultrasonic extraction of particulates collected on glass fiber filters, reverse-phase high-pressure liquid chromatographic separation, and identification and quantitation of the PAH by fluorescence detection at low picogram levels. Precision and accuracy measurements indicate full recovery of PAH and good extraction reproducibility. The detection limit of BP was < 10 picograms. (13 refs)

79-1446 A Rapid In Vitro Assay for Carcinogenicity of Chemical Substances in Mammalian Cells Utilizing an Attachment-Independence Endpoint. (Eng) Traul, K. A. (Pfizer Inc., Maywood, NJ, 07607); Kachevsky, V.; Wolff, J. S. *Int J Cancer* 23(2): 193-196; 1979.

A technique combining growth over an agar medium base and carcinogen-induced transformation of Rauscher leukemia virus (RLV)-infected rat embryo cells resulted in a new assay that allows both preliminary screening for chemical carcinogenicity and transformation confirmation to be completed in 10 days. The method takes advantage of the range of chemical sensitivity of RLV-infected rat embryo cells, but provides for a readout based on the ability of transformed cells to survive under conditions that select for attachment independence. The target cells, 2FR₄50, were treated for 72 hr with a chemical carcinogen and then plated into Petri dishes containing a solid bottom layer of agar medium. Viable cell counts were made 3 and 6 days later and compared with parallel data from solvent-treated control cells. 2FR₄50 cells treated with any of 10 chemical carcinogens, including such diverse compounds as benzo(a)pyrene, 3-methylcholanthrene, 2-acetylaminofluorene, NiSO₄, and urethane, showed an av increase of 225% in survival over controls. Phenanthrene, a noncarcinogen, induced no increase in survival of 2FR₄50 cells. This assay appears to permit the detection of carcinogens of various chemical classes with a simple test readout within 10 days. (20 refs)

79-1447 Increase in Genetic Activity of the Polycyclic Hydrocarbon Benzo(a)pyrene by Inhibition of the Epoxide Hydrase in an Activation System In Vitro. (Eng) Roszinsky-Kocher, G. (Dept. Human Genetics and Anthropology, Universitatstrasse 1, Geb. 23.12, D-4000 Dusseldorf 1, W. Germany); Rohrborn, G. *Mutat Res* 66(2): 199-203; 1979.

The effect of the epoxide hydrase inhibitor cyclohexene oxide (CO) on the genetic activity of benzo(a)pyrene (BP) was stud-

ied in Chinese hamster ovary (CHO) cells with and without a mouse liver homogenate fraction (S9). Cell cultures treated with BP alone did not show any increase in the sister-chromatid exchange (SCE) frequency. The number of metaphases with structural chromosome aberrations increased only when BP was activated. In the presence of the S9 fraction and CO, BP increased the SCE level from 20.3 to 31.1/metaphase, and it also induced structural chromosomal aberrations. The increase in SCE was dose-dependent, but the induction of chromosome aberrations was not. CO alone and CO + BP, but without the S9 fraction, increased the SCE frequency. Based on these results, which are very different from those obtained with 1,1,1-trichloropropane-2,3-oxide (another epoxide hydrazine inhibitor), the effect of CO on the induction of SCE and chromosome aberrations in a BP-metabolizing system was less than expected. The results suggest that epoxides are not the most mutagenic BP metabolites. (11 refs)

- 79-1448 Stereospecificity of Metabolism of Benzo(a)pyrene (BP) to (\pm)trans-7,8-Dihydroxy-7,8-dihydro-BP by Rat Liver Nuclear Enzymes.** (Eng) Jennette, K. W. (Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755); Bornstein, W.; Chuang, A. H.; Bresnick, E. *Biochem Pharmacol* 28(2): 338-339; 1979.

The stereospecificity of the formation of (\pm)trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene (BP 7,8-diol) from benzo(a)pyrene(BP) by rat liver nuclear enzymes was determined using male CD rats pretreated with 3-methylcholanthrene (20 mg/kg ip). The animals were killed 24 hr later, their livers excised, and nuclei isolated. The nuclei were incubated with BP for 30 min, and the metabolites formed were identified by high-pressure liquid chromatography. The results indicated that 92% of the BP 7,8-diol formed by rat liver nuclei was the (-) isomer. The production of (-)-BP 7,8-diol is also > 90% with rat liver microsomal enzymes. Therefore, the stereospecificity of the BP-metabolizing enzymes of the two systems is substantially the same. (24 refs)

- 79-1449 Double-Stranded DNA Stereoselectively Binds Benzo(a)pyrene Diol Epoxides.** (Eng) Meehan, T. (Midland Macromolecular Inst., 1910 W. St. Andrews Drive, Midland, MI, 48640); Straub, K. *Nature* 277(5695): 410-412; 1979.

The enantiomers of (\pm) anti-benzo(a)pyrene (BP) diol epoxide were resolved and reacted with calf thymus DNA. Each enantiomer reacted with the exocyclic amino group of deoxyguanosine to form a pair of diastereomers in a ratio that depended on the secondary structure of the nucleic acid. The (+) enantiomer reacted preferentially or asymmetrically with deoxyguanosine in double-stranded DNA, but the two enantiomers reacted equally with the same position in single-stranded DNA. The basis for the stereoselective binding is unknown, but it may involve formation of sterically oriented physical complexes before covalent attachment of the hydrocarbon to DNA. The mode of binding in the deoxyadenosine

sine sites, on the other hand, must be different, in that the (+) and (-) enantiomers reacted equally in either single- or double-stranded DNA. The results suggest that, in addition to metabolic factors, chemical and physical interactions with DNA may be important in evaluating the biological potency of carcinogenic and aromatic hydrocarbons. (28 refs)

- 79-1450 Interspecies Comparison of Hepatic Mutagenic Activation of Benzo(a)pyrene (BP) (Meeting Abstract).** (Eng) Gordon, G. (Johns Hopkins Sch. Medicine, Baltimore, MD, 21205); DiBlasi, M.; Blake, D. A. *Fed Proc* 38(3, part 1): 534; 1979. (no refs)

- 79-1451 Activation of (+) Trans-7,8-Dihydroxy-7,8-dihydro-benzo(a)pyrene to 7,10/8,9-Tetrols by Prostaglandin Synthetase (Meeting Abstract).** (Eng) Sivarajah, K. (Lab. Pulmonary Function and Toxicology, NIEHS, NIH, Research Triangle Park, NC, 27709); Mukhtar, H.; Eling, T. E. *Fed Proc* 38(3, part 1): 443; 1979. (1 ref)

- 79-1452 Activity of Vitamin K in the Hydroxylation of Benzo(a)pyrene at the 6-Position: A Reevaluation (Meeting Abstract).** (Eng) Sloane, N. H. (Dept. Biochemistry, Univ. Tennessee, Memphis, TN, 38163). *Fed Proc* 38(3, part 1): 723; 1979. (3 refs)

- 79-1453 Effect of Pre-Treatment of Rats with Butylated Hydroxyanisole (BHA) on Benzo(a)pyrene (BP) Pharmacokinetics (Meeting Abstract).** (Eng) Anderson, M. W. (NIEHS, Lab. Pharmacokinetics, Research Triangle Park, NC, 27709); Hirom, P. C.; Boroujerdi, M.; Kung, H. C.; Wilson, A. G. *Fed Proc* 38(3, part 1): 370; 1979. (no refs)

- 79-1454 Reduction of Benzo(a)pyrene Mutagenicity by Dihydrodiol Dehydrogenase.** (Eng) Glatt, H. R. (Section Biochemical Pharmacology, Inst. Pharmacology, Univ. Mainz, D-6500 Mainz, W. Germany); Vogel, K.; Bentley, P.; Oesch, F. *Nature* 277(5694): 319-320; 1979.

The effect of rat liver dihydrodiol dehydrogenase (DD) on the mutagenicity of benzo(a)pyrene (BP) was studied using the microsome/Salmonella test. When BP was activated by liver microsomes from 3-methylcholanthrene-treated mice, addition of pure DD clearly reduced the mutagenicity. The effect increased with DD dose up to 0.5 unit/plate; further addition of DD had no significant effect. Thus, max reduction of mutagenicity was achieved using about 15-fold more enzyme than that present in the amount of liver equivalent to the microsomes used for activation. The degree of BP mutagenicity that could be removed by DD varied with the bacterial strain: with TA98 it was 30%-60%, whereas with TA1537 it was 15%-25%. DD had no effect on BP mutagenicity when microsomes from untreated control mice

were used. Thus, DD can protect against mutagenic effects of BP, but not all the mutagenic metabolites of BP can be removed by DD. (26 refs)

79-1455 Quinone Formation from Benzo(a)pyrene During Cumene Hydroperoxide Interaction with Cytochrome P-450 (448) (Meeting Abstract). (Eng) Capdevila, J. (Dept. Biochemistry, Southwestern Medical Sch., Dallas, TX, 75235); Estabrook, R. W.; Prough, R. *Fed Proc* 38(3, part 1): 527; 1979. (no refs)

79-1456 Effects of Gastrointestinal Hormones on Drug Metabolism in Rat Colon Mucosa Microsomes (Meeting Abstract). (Eng) Fang, W. F. (Univ. Texas Medical Sch., Houston, TX, 77025); Strobel, H. W. *Fed Proc* 38(3, part 1): 365; 1979. (no refs)

79-1457 Effect of Asbestos (Chrysotile Intermediate) on the Metabolism of Benzo(a)pyrene in Syrian Hamster Embryo Cells (Meeting Abstract). (Eng) Eneanya, D. I. (Ohio State Univ. Coll. Medicine, Columbus, OH, 43210); Daniel, F. B.; Hart, R. W. *Fed Proc* 38(3, part 1): 542; 1979. (no refs)

79-1458 The Metabolism of Benzo(a)pyrene in Rabbit Pulmonary Systems (Meeting Abstract). (Eng) Ball, L. M. (Nat'l. Inst. Environmental Health Science, NIH, Research Triangle Park, NC, 27709); Wolf, C. R.; Smith, B. R.; Philpot, R. M.; Bend, J. R. *Fed Proc* 38(3, part 1): 527; 1979. (no refs)

79-1459 Immediate Effect of Cigarette Smoke Inhalation on ¹⁴C-Benzopyrene Metabolism in the Isolated Perfused Rabbit Lung (Meeting Abstract). (Eng) Isaac, R. S. (Coll. Pharmacy, Chandler Medical Center, Univ. Kentucky, Lexington, KY, 40506); Maggard, G. L.; Lubawy, W. C. *Fed Proc* 38(3, part 1): 583; 1979. (1 ref)

79-1460 The Role of Cytochrome P-450 Forms in 2-Aminoanthracene and Benzo(a)pyrene Mutagenesis (Meeting Abstract). (Eng) Norman, R. L. (Scripps Clinic and Res. Foundation, La Jolla, CA, 92037); Muller-Eberhard, U.; Johnson, E. F. *Fed Proc* 38(3, part 1): 535; 1979. (no refs)

79-1461 Benzpyrene Metabolism in Human Diploid Fibroblasts. (Eng) Wohler, W. (I. Medizinische Klinik, Universitat Hamburg, Martinistrasse 52, D-2000 Hamburg 20, W. Germany); Bartram, C. R.; Schurer, C. C.; Rudiger, H. W. *Monogr Hum Genet* 10: 165-170; 1978.

Benzo(a)pyrene (BP) metabolism and the formation of DNA adducts in human diploid fibroblasts increased during 6 hr

of incubation and proceeded linearly thereafter. Confluent cells metabolized about 10 times more BP than exponentially growing fibroblasts. BP was predominantly metabolized via cytochrome P-448-dependent monooxygenase. Evidence that epoxide hydratase might be predominantly involved in the generation of reactive diol epoxides is presented. Both BP metabolism and DNA adduct formation exhibited a broad interindividual variability of more than one order of magnitude in fibroblasts from different donors. (15 refs)

79-1462 Metabolism and Formation of DNA Adducts of Benzo(a)pyrene in Human Diploid Fibroblasts. (Eng) Rudiger, H. W. (I. Medizinische Klinik, Univ. Hamburg, Martinistrasse 52, 2000 Hamburg 20, W. Germany); Marxen, J.; Kohl, F. V.; Melderis, H.; Wichert, P. V. *Cancer Res* 39(3): 1083-1088; 1979.

Variations in the formation of water-soluble metabolites and DNA adducts of benzo(a)pyrene (BP) by skin fibroblast cultures were studied using biopsy material from 29 patients with lung cancer, 7 patients with melanoma, and 28 normal controls. Cultured fibroblasts incubated with G-³H-BP yielded about 10 times more water-soluble metabolites and DNA adducts at stationary growth phase than did proliferating cultures. In all instances, BP metabolism was completely inhibited by α -naphthoflavone (ANF). Trichloropropenoxide and cyclohexenoxide, inhibitors of epoxide hydratase, primarily inhibited the formation of DNA adducts; they had relatively little effect on the formation of water-soluble metabolites. BP turnover in 11 cultures from the same individual showed a coefficient of variation of 40%, which was similar to that of cultures from different donors. However, the ratio of metabolism to DNA adducts in different cultures from the same donor showed a coefficient of variation of only 6.6%. The ratio of water-soluble metabolites to DNA adducts was significantly decreased in cultures derived from lung cancer patients, compared with those derived from melanoma patients or healthy controls. BP metabolism and the formation of DNA adducts in control fibroblasts were correlated with the age of the proband. (44 refs)

79-1463 Benzo(a)pyrene Uptake by Human Plasma Lipoproteins In Vitro (Meeting Abstract). (Eng) Shu, H. P. (Donner Lab., Univ. California, Berkeley, CA, 94720); Nichols, A. V. *Fed Proc* 38(3, part 1): 535; 1979. (no refs)

79-1464 Benzo(a)pyrene Antibody Titers in Sera of Smokers, Ex-Smokers, and Non-Smokers (Meeting Abstract). (Eng) Curtis, G. L. (Dept. Biochemistry, Univ. Nebraska Medical Center, Omaha, NE, 68105); Ryan, W. L. *Fed Proc* 38(3, Part 1): 912; 1979. (2 refs)

79-1465 Ultramicro Analysis of Benzo(a)pyrene in Food. (Eng) Yamaguchi, K. (Faculty Pharmaceutical

Sciences, Univ. Tokyo, Hongo, Tokyo, Japan). *Chem Pharm Bull (Tokyo)* 26(11): 3600-3602; 1978.

The analysis of benzo(a)pyrene (BP) in food by mass-fragmentography (specific ion monitoring by gas chromatography-mass spectrometry) is described. A short (5-10 cm) alkali column at the injection port traps background contaminants, and a column containing the liquid crystal N,N'-[p-butoxybenzyliden]- α,α' -bi-p-toluidine is used to separate BP from benzo(e)pyrene. Two procedures for extracting BP from food with this method are described. (6 refs)

79-1466 Environmental Mutagens in Urban Air Particulates. (Eng) Commoner, B. (Center Biology Natural Systems, Washington Univ., St. Louis, MO, 63130); Madyastha, P.; Bronsdon, A.; Vithayathil, A. J. *J Toxicol Environ Health* 4(1): 59-77; 1978.

The feasibility of using the *Salmonella typhimurium* mutagenesis assay to detect carcinogens in the urban environment was tested by analyzing Chicago air particulates. Extracts of air filter samples were assayed for mutagenicity to *Salmonella* strain TA1538 with and without microsomes prepared from Aroclor-induced rat livers. The extracts contained mutagenicity with and without microsomal activation. Dose-response curves were obtained with extracts of 15 successive samples taken during 1975. The presence of several mutagenic constituents was demonstrated by thin-layer chromatography of particularly active samples, in which the active material was located by mutagenic analysis of successive chromatographic zones. Mass spectrometric analysis of material isolated from an original air filter sample indicated that benzo(a)pyrene and benzo(e)pyrene were present. It is concluded that screening techniques based on the *Salmonella* mutagenicity assay are suitable for analyzing the environmental distribution of organic carcinogens associated with urban air particulates. (9 refs)

79-1467 Methylcobalamin Methylation of Chloroplatinide: Bound Chloride, Valence State, and Relative Mutagenicity. (Eng) Taylor, R. T. (Biomedical Sciences Div., Lawrence Livermore Lab., Univ. California, Livermore, CA, 94550); Happe, J. A.; Wu, R. *J Environ Sci Health A* 13(9): 707-723; 1978.

A methyl-Pt compound formed by incubating K_2PtCl_6 with methylcobalamin (MeB-12) is further characterized physicochemically, and its mutagenicity was compared with that of K_2PtCl_6 and K_2PtCl_4 in auxotrophic Chinese hamster ovary cells (CHO AUXB1). The complexed chloride was determined from nuclear magnetic resonance spectra of the ^{35}Cl -displaced by competing thiocyanate (SCN^-) anions. Release of three chlorides per Pt combined with a Me/Pt ratio of 1.0 indicated a metal coordination number of 4. This is in agreement with x-ray photoelectron spectra, which show that most of the Me-Pt product contains Pt in the +2 valence state. Based on these data and the anionic nature of the product

at pH's from 2.5-7.5, the product is represented as $MePtCl_3^{2-}$. In comparison to the closely related complexes K_2PtCl_6 and K_2PtCl_4 , $MePtCl_3^{2-}$ was slightly less cytotoxic to CHO AUXB1 cells. At concentrations of 15-70 μM , all three compounds induced a 6 to 10-fold increase in the frequency of CHO AUXB1 revertants. Revertants arising either spontaneously (frequency approx 5×10^{-7}) or induced with chloroplatinates or 4-nitroquinoline N-oxide (4-NQO) regained a permanent capacity to grow in medium lacking glycine + adenosine + thymidine. In contrast to the corresponding chloroplatinates, K_2PdCl_4 and K_2PdCl_6 were not mutagenic in CHO AUXB1 as inducers of reversion to prototrophy. They were also 5-10 time less cytotoxic. (13 refs)

79-1468 Disposition of N-(4-Hydroxyphenyl)-All-trans-retinamide in Rats (Meeting Abstract). (Eng) Swanson, B. N. (NIH, Bethesda, MD, 20014); Zaharevitz, D. W.; Frolik, C. A.; Sporn, M. B. *Fed Proc* 38(3, part 1): 265; 1979. (no refs)

79-1469 Species Differences in the Substrate Specificity of Hepatic Cytochrome P-448 from Polycyclic Hydrocarbon-treated Animals. (Eng) Thorgerisson, S. S. (Lab. Chemical Pharmacology, NCI, NIH, Bethesda, MD, 20014); Atlas, S. A.; Boobis, A. R.; Felton, J. S. *Biochem Pharmacol* 28(2): 217-226; 1979.

An attempt was made to determine whether the pattern of α -naphthoflavone (NF) inhibition of selected monooxygenase activities associated with aromatic hydrocarbon responsiveness in the mouse could be used to differentiate among the various forms of cytochrome P-448 in mice, rats, hamsters, guinea pigs, and rabbits. The in vitro effects of NF on aryl hydrocarbon hydroxylase (AAH), 2-acetylaminofluorene N-hydroxylase (AAFH), biphenyl 2-hydroxylase (B2H), and biphenyl 4-hydroxylase (B4H) activities were investigated before and after methylcholanthrene (MC) treatment of C57BL/6N and DBA/2N mice, Sprague-Dawley rats, Syrian hamsters, guinea pigs, and New Zealand white rabbits (all males). The electrophoretic pattern of cytochrome P-450 subunits and the reduced CO-hemoprotein difference spectra of the microsomal fractions were also studied. Pretreatment of animals with MC caused: (1) a 1.5- to 2-mm hypsochromic shift in the Soret peak of the reduced hemoprotein-CO complexes in liver microsomes from C57BL/6N mice, rats, hamsters, and rabbits; a 0.5-nanometer hypsochromic shift in guinea pigs and no shift in DBA/2N mice; and (2) an increase in cytochrome P-450 apoproteins of the following mol wts upon sodium dodecyl sulfate-polyacrylamide gel electrophoresis: 54,000 (54K) and 55K in C57BL/6N mice; 48K, 54K, and 55K in rats; 49K and 54K in hamsters; and 54K and 57K in rabbits. A small increase in the 54K band was seen in DBA/2N mice and no increase was seen in guinea pigs. In vitro addition of α -NF selectively inhibited all four monooxygenase activities in MC-treated C57BL/6N mice, rats, and hamsters; 2-AAFH and B4H activities in rabbits; and AAH, AAFH, and B4H activities in guinea pigs. NF

enhanced AAH and B2H activities in liver microsomes from both control and MC-treated rabbits, but only B2H activity in guinea pigs. AAFH activity was increased in both control and MC-treated DBA/2M mice, but only in control C57BL/6N mice. These data indicate that hepatic cytochrome P-448 is composed of multiple cytochromes that differ among animal species, each catalyzing different monooxygenase activities. (35 refs)

79-1470 The Effect of Isolation Stress on Some Carcinogen-Metabolising Enzyme Systems of Rats.

(Eng) Capel, I. D. (Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey RH8 0TL, England); Williams, D. C. *IRCS Med Sci (Cancer)* 7(1): 14; 1979.

In male Sprague-Dawley rats, isolation stress (ie, isolation in darkened boxes for 2-8 days) increased the activity of enzymes responsible for the metabolic activation of carcinogens but did not affect their excretion. This treatment increased plasma cortisol levels and aryl hydrocarbon hydroxylase activity, but it did not affect uridine diphosphoglucuronic acid transferase levels. (5 refs)

79-1471 Dietary Protein, Aryl Hydrocarbon Hydroxylase and Chemical Carcinogenesis in Rats. (Eng)

Clinton, S. K. (Sch. Basic Medical Sciences, Univ. Illinois, Urbana, IL, 61801); Truex, C. R.; Visek, W. J. *J Nutr* 109(1): 55-62; 1979.

The relationships between dietary protein concentration (7.5%, 15%, or 45%) to changes in hepatic aryl hydrocarbon hydroxylase (AHH) activity and 7,12-dimethylbenz(a)anthracene (DMBA, 2 mg/g in a single po dose) mammary carcinogenesis were studied in female Sprague-Dawley rats. The specific activity and activity per gram of body wt of AHH, cytochrome P-450, and NADPH cytochrome c reductase increased as the percentage of protein in the diet increased. The incidence of palpable mammary tumors in DMBA-treated rats was inversely related to the dietary protein concentration prior to carcinogen treatment, being 75% in the 7.5% protein group, 44% in the 15% group, and 25% in the 45% group at 25 wk. The period between DMBA administration and detection of palpable tumors, the percentage of tumor-bearing rats with multiple tumors, and the number of tumors per tumor-bearing rat were also inversely related to dietary protein concentration. Dietary protein concentration following DMBA treatment had no significant effect on tumor incidence or latency. The results support the hypothesis that increasing dietary protein may decrease the concentration of potential carcinogenic DMBA metabolites reaching the mammary gland by stimulating the hepatic metabolism of DMBA. (46 refs)

79-1472 Aryl Hydrocarbon (Benzo[a]pyrene) Hydroxylase Development in Rat Mammary Tissue.

(Eng) Fysh, J. M. (Dept. Biology, Univ. Windsor, Windsor,

Ontario, Canada N9B 3P4); Okey, A. B. *Biochem Pharmacol* 27(24): 2968-2972; 1978.

The ontogeny of aryl hydrocarbon hydroxylase (AHH), its inducibility by β -naphthoflavone (BNF: 80 mg/kg, ip, for 2 days prior to sacrifice at ages 22-444 days), and its inhibition by α -naphthoflavone (ANF: 10 μ M) were studied in female Sprague-Dawley rats. An attempt was made to determine the capacity of mammary tissue to metabolize benzo(a)pyrene (BP) and to determine whether age-related variations in mammary AHH activity are related to susceptibility to polycyclic aromatic hydrocarbon (PAH)-induced carcinogenesis. In control rats, AHH activity was high at ages 28-35 days, but it decreased to lower levels by 42 days. Addition of ANF to the microsomal incubation mixture produced an approx 35% inhibition of basal AHH activity. Ovariectomy of control rats produced a twofold increase in AHH activity but had no effect on induction of AHH by BNF. Phenobarbital pretreatment (80 mg/kg/day for 3 days, ip) only slightly increased mammary AHH activity. The ratio of BNF-induced activity:control activity varied with the age of the rats, ranging from 6- to 70-fold for mammary tissue and 11- to 36-fold for liver tissue. ANF inhibited BNF-induced AHH activity by about 60%, especially at ages when inducibility was highest (91-262 days). The data suggest that no simple relationship exists between mammary or liver AHH activity and age-related differential sensitivity to carcinogenesis by PAH. (16 refs)

79-1473 Epoxide Hydrase and Mixed-Function Oxidase Activities of Rat Liver Nuclear Membranes.

(Eng) Mukhtar, H. (Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709); Elmamlouk, T. H.; Bend, J. R. *Arch Biochem Biophys* 192(1): 10-21; 1979.

The specific cytochrome P-450 levels and aryl hydrocarbon hydroxylase (AHH), aminopyrine N-demethylase, benzphetamine N-demethylase, NADPH-cytochrome c reductase, and epoxide hydrase activities were compared in hepatic microsomes, nuclei, and nuclear membranes prepared from male Sprague-Dawley rats. Nuclear activity ranged from 1.8% (for NADPH-cytochrome c reductase) to 11.3% (for AHH) of the microsomal activity. The specific activity of the various parameters measured in nuclear membranes ranged from 1.3-fold (for cytochrome P-450) to 10.2-fold (for NADPH-cytochrome c reductase) greater than that in intact nuclei. Nuclear and microsomal epoxide hydrases were both induced by phenobarbital but not by 3-methylcholanthrene. Nuclear membrane and microsomal epoxide hydrase were both inhibited to a similar degree by 1,1,1-trichloropropene oxide, cyclohexene oxide, and trans-stilbene oxide. The apparent K_m value for nuclear membrane epoxide hydrase was 20 μ M for benzo(a)pyrene 4,5-oxide, which is 5.5-fold lower than the corresponding microsomal K_m value (112 μ M). Epoxide hydrase in intact nuclei from various organs was in the following order: kidney > lung > spleen or heart. Increases of 2.2- and 2.5-fold in specific hydrase activity were

detected in kidney and lung when nuclear membranes were compared with intact nuclei. The presence of significant monooxygenase and epoxide hydrase activities in the nucleus is consistent with a role in the bioactivation of environmental pollutants to carcinogenic and/or mutagenic products. (47 refs)

- 79-1474 The Role of Diethylstilbestrol Metabolism in Its Binding to Fetal and Maternal Tissues (Meeting Abstract).** (Eng) Miller, R. K. (Dept. Obstetrics, Univ. Rochester, Rochester, NY); McKenzie, R. C. *Fed Proc* 38(3, part 1): 438; 1979. (1 ref)

- 79-1475 Activity of Aryl Hydrocarbon Hydroxylase in Psoriatic Skin.** (Eng) Chapman, P. H. (Dept. Pharmacological Sciences, Wolfson Unit, Claremont Place, Univ. Newcastle upon Tyne, Newcastle upon Tyne NE1 7RU, England); Rawlins, M. D.; Shuster, S. *Lancet* 1(8111): 297-298; 1979.

The activity of aryl hydrocarbon hydroxylase (AHH) in the normal and psoriatic epidermis from 20 patients with psoriasis was compared with that in epidermis from 13 normal subjects using benzo(a)pyrene as substrate. Induction of epidermal AHH activity by benzantracene (BA) was also measured. In the absence of BA, AHH activity was significantly lower in epidermis from psoriatic lesions [1.84 picomoles (pmol) 3-hydroxybenzo(a)pyrene/mg protein/hr] and normal epidermis from psoriasis patients (2.41 pmol) than in epidermis from normal subjects (3.41 pmol). Preincubation with 100 micromoles/liter of BA significantly increased the absolute activity of AHH in epidermis from normal subjects and increased it significantly but to a lesser extent in the uninvolved epidermis of psoriatic patients. The epidermis from psoriatic lesions showed no induction of AHH in response to BA. The enzyme defect in the psoriasis patients may be related to the primary genetic abnormality of the disease. Since AHH activity is a major factor in chemical carcinogenesis, the risk of skin cancer, and perhaps cancers of other organs, may be reduced in individuals with psoriasis. (4 refs)

- 79-1476 High-Pressure, Reverse-Phase Partition Chromatography Separation of Diethylstilbestrol Metabolites and Analogs.** (Eng) Gottschlich, R. (Inst. Toxicology, Univ. Wurzburg, Versbacher Landstrasse 9, D-8700 Wurzburg, W. Germany); Metzler, M. *Anal Biochem* 92(1): 199-202; 1979.

Various conjugated and oxidative metabolites of diethylstilbestrol (DES) were separated by high-pressure, reverse-phase liquid chromatography on C_8 - and C_{18} -hydrocarbon phases with water-methanol gradients. The compounds separated included metabolites such as 4'-hydroxy-propiophenone, 3'-hydroxy-DES, β -dienestrol, and ω -hydroxy- β -dienestrol. (10 refs)

- 79-1477 Species and Organ Specificity of the trans-Stilbene Oxide Induced Effects on Epoxide Hydratase and Benzo(a)pyrene Monooxygenase Activity in Rodents.** (Eng) Oesch, F. (Section Biochemical Pharmacology, Inst. Pharmacology, Univ. Mainz, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany); Schmassmann, H. *Biochem Pharmacol* 28(2): 171-176; 1979.

The effect of trans-stilbene oxide (TSC) on epoxide hydratase (EH) and benzo(a)pyrene monooxygenase (BPMO) activity was investigated in the liver, kidney, lung, skin, and testis of rats, mice, and hamsters. Adult male and female Sprague-Dawley rats, male Syrian Golden hamsters, and male NMRI mice were treated with 0.2, 0.5, or 2.0 millimoles (mmol)/kg ip 1x/day for 3 days. The animals were killed 24 hr later and the microsomal enzyme activities determined. The ability of TSO to induce liver EH activity, expressed as percent of controls, was 350%, 180%, and 140% in the rat, mouse, and hamster, respectively. In the rat livers, EH activity was induced to 300%-400% of controls after treatment with 2.0 mmol TSO, but BPMO activity was not affected. Selective induction of EH was also found in hamster liver but not in mouse liver, in which BPMO activity was induced to about the same extent as EH activity. The only extrahepatic organ in which EH activity was increased after TSO treatment was the rat kidney, but the extent of induction was lower than that in the liver. Topical and sc treatment with TSO for 10 and 12 days, respectively, decreased EH activity in rat skin to 70% of that found in control animals. Thus, applicability of TSO to investigations of the role of EH in the metabolism of polycyclic hydrocarbons is limited to systems in which rat liver can be used. (33 refs)

- 79-1478 Variability of Response to Diethylstilbestrol: A Comparison of Inbred with Hybrid Mice.** (Eng) Greenman, D. L. (Div. Molecular Biology, Natl. Center Toxicological Res., Jefferson, AR, 72079); Delongchamp, R. R.; Highman, B. *J Toxicol Environ Health* 5(1): 131-143; 1979.

The uterine and thymic wt responses to diethylstilbestrol (DES) were examined in BALB/cStCrIFC3Hf/Nctr, C57BL/6JfC3Hf/Nctr, [C57BL/6 x BALB/c]F₁ hybrid (F₁), and monohybrid cross offspring (F₂) from the breeding of F₁ mice. Approx 400 weanling females from each genetic population were exposed for 6 days to DES (2.5-1,000 ppb in the diet). Uterine wt variances for the BALB/c and F₁ mice were indistinguishable from each other and significantly smaller than variances for the F₂ and C57BL/6 mice. Thymic wt variances were also smallest for BALB/c and F₁ mice and highest for C57BL/6 mice. In a chronic feeding study, body wt responses were examined and gross necropsy observations were recorded for the pituitaries and testes of 576 mice of each genetic population given 5-640 ppb DES. The dose-response effect on body wt was examined at 30 wk in males and 60 wk in females. Variances were smallest for BALB/c mice and largest for F₂ hybrids. Those for F₁ and C57BL/6 mice were intermediate and indistinguishable from each other. Gross necropsy of animals dead or moribund dur-

ing the first 15 mo of DES exposure indicated the following: (1) at 15 mo, pituitary and testicular responses were visible only at ≥ 160 ppb DES; (2) BALB/c males developed mainly testicular lesions but C57BL/6 mice developed pituitary lesions; and (3) F₁ and F₂ animals developed both types of lesions and were not different from each other in this respect. It is concluded that generalizations cannot be used in selecting the best experimental animal for a specific purpose. (12 refs)

79-1479 Influence of Diethylstilbestrol Treatment on Prolactin Cells of Female ACI and Sprague-Dawley Rats. (Eng) Holtzman, S. (Medical Dept., Brookhaven Natl. Lab., Upton, NY, 11973); Stone, J. P.; Shellabarger, C. J. *Cancer Res* 39(3): 779-784; 1979.

Pellets containing 5 mg diethylstilbestrol (DES) and 15 mg cholesterol were implanted in female ACI and Sprague-Dawley (S-D) rats for periods ranging from 2 to 214 days. In view of the differences between these two strains in mammary tumorigenesis, plasma prolactin (PL) levels, and gross pituitary (Pt) responses, the cytology of Pt glands that were fixed during the course of this study was examined and an immunohistochemical evaluation was made of their PL cell responses. Although plasma PL levels were elevated in both strains by 2 days after implantation, during the first 10 days of treatment there were no significant increases in Pt wt in both strains. Pt glands from animals of both strains killed on day 10 exhibited enlarged anti-rat PL-binding cells. By day 28, the Pt glands of DES-treated ACI rats were significantly enlarged, and a hypertrophic and hyperplastic response of their PL cells was detected. From day 56 to the end of the experiment, gross Pt tumorigenesis was evident in the ACI but not in the S-D rats. At the microscopic level, adenomatous lesions involving PL cell hyperplasia were observed in both strains. S-D and ACI rats exhibited multiple centers of marked vascularization predominated by granular acidophilic cells. These centers were more extensive and larger in the Pt's of the ACI rats. Two types of immunoreactive PL cells were observed in lesioned Pt glands of both strains: polyhedral, strongly reactive cells that were hypertrophic and more numerous in the ACI rats; and smaller, weakly reactive cells that were numerous in the adenomatous areas of the glands in both strains. It was concluded that the lesions in ACI and S-D females represented different quantitative responses of their PL cells to DES treatment. (20 refs)

79-1480 Neoplastic Responses and Correlated Plasma Prolactin Levels in Diethylstilbestrol-treated ACI and Sprague-Dawley Rats. (Eng) Stone, J. P. (Medical Dept., Brookhaven Natl. Lab., Upton, NY, 11973); Holtzman, S.; Shellabarger, C. J. *Cancer Res* 39(3): 773-778; 1979.

The relationships between estrogen treatment, prolactin (PL) levels, mammary (Ma) development, and neoplasia induction in the Ma tissue and pituitary (Pt) glands of female Sprague-Dawley (S-D) and ACI rats were investigated. Pellets

containing 5 mg diethylstilbestrol (DES) and 15 mg cholesterol were implanted sc in 84-day-old rats. [G-³H]DES (32.9 nanocuries/mg DES) was incorporated into each pellet. Animals were decapitated, blood was collected at various times after implantation, and the amount of [G-³H]DES remaining in each pellet was determined. Plasma PL levels were determined by radioimmunoassay. DES was released from the pellets exponentially, and the release was not significantly different in S-D rats than in ACI rats. No Ma tumors developed in any treated or untreated S-D rats. In contrast, 90% of the treated ACI rats had developed two or more Ma adenocarcinomas by 130 days, and by 214 days, 90% had four or more Ma adenocarcinomas. Pt wt increased significantly in treated ACI rats by 28 days. By day 130, the Pt's were 2-7 times as heavy as those of controls, and plasma PL levels were 10-40 times higher than those in controls. In contrast, the Pt's of treated S-D rats did not increase significantly in wt, and plasma PL levels were only three to five times higher than of those controls. As early as day 10, the uteri of treated S-D rats were significantly heavier than those of controls, and they contained large amounts of fluid. This effect was not seen in ACI rats. Although the release of DES from the implanted pellet was essentially the same in ACI and S-D rats, three distinctive strain differences in response to DES were noted: Ma adenocarcinomas were found only in ACI rats; Pt PL cell adenomas and associated elevated plasma PL levels were seen only in ACI rats; and pyometritis was induced only in S-D rats. Ma adenocarcinomas and PL cell adenoma responses in the treated ACI rats appear to be correlated with the increasing levels of plasma PL. Thus, prolonged estrogen treatment of ACI and S-D female rats produces distinctly different Ma and Pt neoplastic responses. This disparity in neoplastic responses appears to be reflected in the difference of degree to which the hypophyseal PL cells are stimulated to grow and secrete hormone. (35 refs)

79-1481 Cytological Effects of Diethylstilbestrol (DES) Treatment on the Estrous Cycle of Virgin Long-Evans Female Rats. (Eng) Okediji, O. (Dept. Biology, Atlanta Univ., Atlanta, GA, 30314); Hunter, R. *IRCS Med Sci (Cancer)* 7(1): 28; 1979.

Diethylstilbestrol (DES) treatment (35 mg/2 ml saline/kg body wt by stomach intubation) produced a secondary effect--asynchronous cell proliferation in the vaginal epithelia of virgin Long-Evans rats, leading to prolonged specific stages of the estrous cycle. Two rats remained in persistent estrous for 25 days after treatment, and two others remained in persistent proestrous for 13 days. A further two rats remained in diestrous 13 days after treatment. (6 refs)

79-1482 Transplacental Effect of Diethylstilbestrol in Female Rats. (Eng) Napalkov, N. P. (Petrov Res. Inst. Oncology, 68 Leningradskaya St., Pesochny-2, Leningrad 188646, USSR); Anisimov, V. N. *Cancer Lett* 6(2): 107-114; 1979.

The transplacental effect of diethylstilbestrol propionate (DES; 1 mg/kg sc) was studied in the female offspring of random-bred albino rats exposed sc on gestation day 19. Examination of vaginal smears showed persistent estrus in adult rats treated prenatally with DES. Compensatory ovarian hypertrophy (COH) induced by hemicastration of these rats was not suppressed by estrogens (DES: 0.57 μ g/day x 7, sc). A po test for glucose tolerance revealed decreased utilization of glucose in the offspring of DES-treated rats. Tumors developed in 14/18 progeny transplacentally exposed to DES and 9/34 intact control rats. Tumors of the ovary and the endometrium were found only in the rats treated prenatally with DES; no tumors of the uterine cervix or vagina were observed in either experimental or control groups. It is suggested that transplacental exposure to DES impairs the sex differentiation of the hypothalamus in female rats. The resulting hormonal and metabolic shifts might promote tumorigenesis. (30 refs)

79-1483 Detection of Diethylstilbestrol in the Urine of Calves and Young Cattle by Thin-Layer Chromatography. (Ger) Schellhaas, G. (Landesveterinaruntersuchungsamt für Rheinland-Pfalz, Blucherstrasse 34, 5400 Coblenz, W. Germany); Kleickmann, A.; Nitzschke, E. *Arch Lebensmittelhyg* 29(6): 219-222; 1978.

Three 9- to 10-mo-old calves were treated with diethylstilbestrol (DES) im, and urine samples were analyzed for excreted estrogen by thin-layer chromatography. DES was detected in the urine of a female calf for up to 22 days after the administration of 50 mg and in the urine of two male calves for up to 11 days after the administration of 60 and 70 mg, respectively. (5 refs)

79-1484 Accretion of Biopsy Specimens of Vaginal Adenosis from Patients Exposed In Utero to Diethylstilbestrol, When Transplanted to Athymic Nude Mice. (Eng) Pienkowski, M. M. (Dept. Anatomy, Michigan State Univ., E. Lansing, MI, 48824); Mann, L. C.; Rosloniec, E. F.; Welsch, C. W. *J Natl Cancer Inst* 62(3): 521-523; 1979.

The successful transplantation of biopsy specimens of human vaginal adenosis into female athymic (nude) mice is reported. Biopsy specimens from 10 patients exposed in utero to diethylstilbestrol were transplanted for 30 days into the mice. Almost all grafts were recovered, and they had morphologic features closely resembling those of the original biopsy specimens; ie, cystic, complex, and simple occult glands covered mainly with an endocervical type of epithelium showing extensive squamous metaplasia. Autoradiographic analysis of these grafts after pulse administration of [3 H]thymidine into the mice revealed extensive labeling of epithelial cells. These results imply that female athymic (nude) mice are compatible hosts for accretion of the human adenosis. (24 refs)

79-1485 Effects of Perinatal Testosterone on Mouse Mammary Duct Morphology and Lobule Induc-

tion In Vitro. (Eng) Warner, M. R. (Cancer Res. Lab., Univ. California, Berkeley, CA, 94720). *Cancer Res* 39(3): 744-750; 1979.

The effects of several hormone supplements to the chemically defined medium were assessed in mammary explants from C57BL/Crgl mice that had been inoculated sc with 25 μ g testosterone (TS) on each of the first 5 days of life and in mammary tissues of untreated controls. Tissues were organ-cultured in the fourth week of life after 4, 6, and 9 days of pretreatment with 1 μ g 17 β -estradiol (ED) + 1 mg progesterone (PG). Alveolar and lobular development were similar in tissues of perinatally TS-injected (TS-I) mice and their controls after in vivo pretreatment and after 4 or 9 days of pretreatment followed by culture in all media tested. Both alveolar and lobular development were inhibited in tissues from TS-I mice after 6 days of pretreatment followed by culture with optimal medium for lobular differentiation (ED, PG, aldosterone, growth hormone, prolactin, insulin, and thyroxine). After 6 days of pretreatment, explants from TS-I mice responded similarly to controls after culture with suboptimal media (insulin and thyroxine, or estrogen, PG, aldosterone, insulin, and thyroxine). Perinatal injection of TS, a treatment that has been reported to promote mammary tumorigenesis, did not promote in vitro differentiation of mammary lobules; indeed, significant inhibition of lobule formation was noted after 6 days of pretreatment. A 6-day minimal threshold effect for expression of pretreatment may be involved. Duct diameter increased in explants from TS-I mice after culture in several medium and pretreatment groups. Differences in duct responses were markedly uniform throughout the explant in cultured tissues of TS-I mice. In view of the fact that mammary ducts have been implicated as sites of origin of preneoplastic and neoplastic change, duct responses are of particular interest in relation to subsequent promotion by various endogenous and exogenous factors of the neoplastic potential of mammary tissues of perinatally TS-I mice. (29 refs)

79-1486 Inhibition of Spontaneous Breast Cancer Formation in Female C3H (A ν y/a) Mice by Long-Term Treatment with Dehydroepiandrosterone. (Eng) Schwartz, A. G. (Fels Res. Inst., Temple Univ. Medical Sch., Philadelphia, PA, 19140). *Cancer Res* 39(3): 1129-1132; 1979.

The effects of long-term treatment of 24 weanling female 3CH (A ν y/a) mice with dehydroepiandrosterone (DHEA: 450 mg/kg in sesame oil 3x/wk by po intubation) on spontaneous breast cancer formation was investigated. The 26 control mice received vehicle only. All mice were weighed and palpated for breast cancer weekly. Food consumption was also monitored. The wt gain of the DHEA-treated mice was significantly lower than that of controls at all times after 9 wk of age, even though the cumulative food consumptions of the two groups were not significantly different. Substantial inhibition of mammary gland glucose-6-phosphate dehydrogenase activity was observed at 3, 6, and 24 hr after

DHEA treatment. As of 9 mo of age, the cumulative breast cancer incidence was 0/24 treated mice vs 14/26 controls. These results may be related to the clinical findings of subnormal mean plasma levels of DHEA sulfate in preoperative and postoperative early breast cancer patients as well as in those with advanced disease. (29 refs)

79-1487 Suppression of Pregnancy and Estrogen-Progesterone Induced Mammary Tumorigenesis in Female GR Mice by Chronic Inhibition of Prolactin Secretion (Meeting Abstract). (Eng) Goodrich-Smith, M. A. (Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824); Brown, C. K.; Welsch, C.W. *Fed Proc* 38(3, part 2): 1256; 1979. (no refs)

79-1488 Attempts to Induce Gonadotropic Tumors (GtT); Immunohistochemical Observations on the Pituitaries of Long Term Gonadectomized Rats (Meeting Abstract). (Eng) Kaul, D. K. (Coll. Physicians and Surgeons Columbia Univ., New York, NY, 10032); Furth, J. *Fed Proc* 38(3, part 1): 1025; 1979. (no refs)

79-1489 Action of Local Progesterone on Benign Breast Disease (500 Case Studies). (Fre) Lafaye, C. (Service des Methodes Physiques, Centre Jean Perrin, Place Henri Dunant, B.P. 392, 63011 Clermont Ferrand Cedex, France); Aubert, B. *J Gynecol Obstet Biol Reprod (Paris)* 7(6): 1123-1139; 1978.

The effect of progesterone treatment was studied in 250 women with mastodynia, 190 women with mastodynia associated with benign pathological changes, and 60 women with painless, benign, pathological changes in the breast. Progesterone was administered topically, daily for 3 mo. Thermography was carried out in each patient before and after treatment. After treatment, the symptoms disappeared completely in 70% of the patients with isolated mastodynia, and the clinical condition improved in an additional 15%. The thermographic features, which were abnormal in these patients before treatment, were normal in 78% of cases and were improved in an additional 19%. Thus, the clinical results were considered excellent or good in a total of 85% of the patients with isolated mastodynia, and the thermographic results were con-

sidered excellent or good in a total of 97%. The thermogram was normal following treatment in 70% of the patients with mastodynia associated with breast disease, and the clinical condition returned to normal in 50%. The clinical condition improved in a further 17%, and thermographic improvement was observed in a further 19%. In patients with breast disease without mastodynia, clinical and thermographic improvement was seen in 10% and 20%, respectively, after progesterone treatment. The results demonstrate that progesterone treatment is useful in the treatment of benign breast conditions. (40 refs)

See also:

- *(Rev.): 79-1202, 79-1203, 79-1204, 79-1205, 79-1206, 79-1207, 79-1208, 79-1209, 79-1210, 79-1211, 79-1212, 79-1213, 79-1214, 79-1215, 79-1216, 79-1217, 79-1218, 79-1219, 79-1220, 79-1221, 79-1222, 79-1223, 79-1224, 79-1225, 79-1226, 79-1227, 79-1228, 79-1229, 79-1230, 79-1231, 79-1232, 79-1233, 79-1234, 79-1235, 79-1236, 79-1237, 79-1248, 79-1262, 79-1266, 79-1274, 79-1276, 79-1281, 79-1284, 79-1286, 79-1288, 79-1289, 79-1293, 79-1294, 79-1297, 79-1301, 79-1302, 79-1304.
- *(Phys.): 79-1493, 79-1494, 79-1495, 79-1496, 79-1501, 79-1504, 79-1509, 79-1521, 79-1530, 79-1532.
- *(Viral): 79-1548, 79-1554, 79-1559, 79-1580, 79-1596, 79-1639.
- *(Immun.): 79-1664, 79-1666, 79-1667, 79-1671, 79-1680, 79-1686.
- *(Path.): 79-1695, 79-1703, 79-1724.
- *(Epid.-Biom.): 79-1739, 79-1740, 79-1744, 79-1745, 79-1746, 79-1747, 79-1748, 79-1749, 79-1750, 79-1751, 79-1754, 79-1758, 79-1759, 79-1765, 79-1767, 79-1768, 79-1769, 79-1771, 79-1776, 79-1780.

PHYSICAL CARCINOGENESIS

- 79-1490 Induction of Mouse Epidermal Ornithine Decarboxylase Activity and DNA Synthesis by Ultraviolet Light.** (Eng) Verma, A. K. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706); Lowe, N. J.; Boutwell, R. K. *Cancer Res* 39(3): 1035-1040; 1979.

Changes in epidermal ornithine decarboxylase (ODC) activity were investigated following exposure of female hairless mice (HKH/Hr) to UV radiation. Irradiation of the mice with UV light of mainly the sunburn region [region of UV light with a wavelength of 290-320 nanometers (UVB)] resulted in a dramatic increase in epidermal ODC activity. A significant increase in enzyme activity was observed as early as 2 hr following UVB exposure. Max activity, about 250- to 350-fold above basal level, occurred at about 28 hr. ODC activity declined steadily thereafter, but it had not returned to the original level even at 48 hr after UVB irradiation. UVB treatment also led to an increased activity of S-adenosyl-L-methionine decarboxylase, a second enzyme in the pathway of polyamine biosynthesis. Enzyme activity was increased at about 6 hr and remained elevated at 48 hr after exposure to UVB. UVB-induced epidermal ODC activity was depressed by treatment of mice with cycloheximide, an inhibitor of protein synthesis, or with 5-azacytidine, an inhibitor of RNA synthesis. The half-life of UVB-induced ODC was found to be about 24 min, as determined by the decline of enzyme activity after cycloheximide treatment. Incorporation of tritiated thymidine into epidermal DNA was initially depressed, and a four-fold increase at 48 hr after UVB exposure was observed. Histological examination of UVB-treated skin revealed epidermal thickening by 48 hr. These studies show that irradiation with UVB, the most carcinogenic region of UV light, induces mouse epidermal ODC activity, and that the elevated enzyme activity precedes increased epidermal DNA synthesis. (26 refs)

- 79-1491 DNA Damage in Synchronized HeLa Cells Irradiated with Ultraviolet.** (Eng) Downes, C. S. (Dept. Zoology, Univ. Cambridge, CB2 3EJ Cambridge, England); Collins, A. R.; Johnson, R. T. *Biophys J* 25(1): 129-150; 1979.

The lethal effect of UV radiation on HeLa cells was found to be least in mitosis and greatest in the late G₁ through early S phase. Photochemical damage to HeLa cell DNA also increased from mitosis toward early S. Computer simulations of UV absorption by an idealized HeLa cell at different stages of the cell cycle indicated that UV sensitivity may be a function of chromatin geometry, although survival is not exclusively a function of damage. (77 refs)

- 79-1492 UV Irradiation Stimulates Synthesis of Poly(adenosine Diphosphoribose) in Associa-**

tion with DNA Repair (Meeting Abstract). (Eng) Berger, N. A. (Jewish Hosp., St. Louis, MO, 63110); Sikorski, G. W.; Petzold, S. J.; Kurohara, K. K. *Fed Proc* 38(3, part 1): 619; 1979. (no refs)

- 79-1493 Repair of Ultraviolet Radiation- and N-Acetoxy-2-acetylaminofluorene-induced DNA Damage in Permeabilized Human Cells (Meeting Abstract).** (Eng) Roberts, J. D. (Washington Univ. Sch. Medicine, St. Louis, MO, 63110); Lieberman, M. W. *Fed Proc* 38(3, part 2): 1404; 1979. (no refs)

- 79-1494 Effects of DNA Damaging Agents on Cultured Fibroblasts Derived from Patients with Cockayne Syndrome.** (Eng) Wade, M. H. (Medical Biological Labs. T.N.O., Lange Kleiweg 139, P.O. Box 45, 2280 AA Rijswijk [Z.H.], Netherlands); Chu, E. H. *Mutat Res* 59 (1): 49-60; 1979.

The cytotoxicity of various physical and chemical agents in skin fibroblast cultures derived from 10 patients with Cockayne's syndrome (CS), 4 parents of CS patients, 2 patients with xeroderma pigmentosum (XP), and 2 normal subjects was studied. The CS cell strains were significantly more sensitive to UV light than the normal cells, with the strains derived from the CS parents being intermediate in UV sensitivity. Caffeine (0.5 mM) had no effect on the UV sensitivity of normal or CS cells, but it increased the UV sensitivity of XP cells. DNA repair synthesis following UV irradiation was similar in normal and CS cells, but it decreased in XP cells. The colony-forming ability of CS and XP cells exposed to N-acetoxy-2-acetylaminofluorene or 4-nitroquinoline-1-oxide differed significantly from that of normal cells, whereas ethyl methanesulfonate and 2-methoxy-6-chloro-9-[3-(ethyl-2-chloroethyl)aminopropylamino]acridine dihydrochloride had similar effects on the colony-forming abilities of CS, XP, and normal cells. The data suggest that excision repair is deficient in patients with CS. (33 refs)

- 79-1495 Excision Repair in Ataxia Telangiectasia, Fanconi's Anemia, Cockayne Syndrome, and Bloom's Syndrome after Treatment with Ultraviolet Radiation and N-Acetoxy-2-acetylaminofluorene.** (Eng) Ahmed, F. E. (Dept. Biology, Brookhaven Natl. Lab., Upton, NY, 11973); Setlow, R. B. *Biochim Biophys Acta* 521(2): 805-817; 1978.

Excision repair of damage due to UV radiation and/or N-acetoxy-2-acetylaminofluorene (AAF) was studied in normal human fibroblasts and various cells from cancer-prone patients with ataxia telangiectasia, Fanconi's anemia, Cock-

ayne's syndrome, or Bloom's syndrome. Measurements were made of unscheduled DNA synthesis, photolysis of bromodeoxyuridine incorporated into parental DNA during repair, and loss of sites sensitive to UV endonuclease. The results indicated that all cell lines were equally proficient in repair of damage caused by UV irradiation and/or AAF. All cell lines showed an additive effect for the combined treatment, and there was quantitative equivalence between UV and AAF as far as the level of repair was concerned. The data indicated that the rate-limiting step in excision repair of UV and AAF damage is different and that there are different enzyme(s) working on the incision of both types of damage. (37 refs)

79-1496 Biochemical Analysis of the Response of Mammalian Cells to UV Light and Sunscreen Agents (Meeting Abstract). (Eng) Long, S. D. (Harvard Sch. Public Health, Boston, MA, 02115); Little, J. B. *Fed Proc* 38 (3, part 1): 846; 1979. (no refs)

79-1497 Some Effects of the Variation of Atmospheric Particulates on Disease in Great Britain. (Eng) Leach, J. F. (Weybridge-Bristol Div., British Aerospace, Filton, Bristol, England); Beadle, P. C.; Pingstone, A. R.; Aughton, P. *Aviat Space Environ Med* 50(1): 72-79; 1979.

The possible UV radiation changes that might have followed from the reduced particulate concentration resulting from the UK Clean Air Acts of 1965 and 1968 are considered by making assumptions as to the nature of the aerosols in the Bristol, England, area and calculating their extinction coefficients. These calculations indicate that both carcinogenic and calciferogenic UV radiation could have increased by an amount approx equivalent to a 10% decrease in the total ozone column. The effect of these radiation changes is detectable in the increased mortality from epitheliomas in the Bristol area and the decrease in femoral neck fracture in England and Wales. Extrapolating these findings to a highly polluted environment, such as that in Los Angeles, suggests that implementation of the US Air Quality Act and Clean Air Amendments of 1970 must result in a significant increase in epitheliomas in the Los Angeles area without compensation from a reduced incidence of vitamin D deficiency disease. (21 refs)

79-1498 Sunlight and Incidence of Cutaneous Malignant Melanoma. Effect of Latitude and Domicile in Sweden. (Eng) Eklund, G. (Dept. Statistics, Univ. Stockholm, Stockholm, Sweden); Malec, E. *Scand J Plast Reconstr Surg* 12(3): 231-241; 1978.

To determine the relationship between exposure to sunlight and the development of cutaneous malignant melanoma (CMM), habitation patterns were investigated for 3,289 CMM patients who were registered between 1959 and 1968 in the Swedish Cancer Registry. The correlation coefficient between latitude and CMM incidence was -0.74, implying

that incidence decreases with increasing latitude and supporting the hypothesis that UV radiation is the predominant cause of melanoma. However, considerable deviations from the regression line were noted in some regions. In addition, analysis of the incidence per 100,000 inhabitants showed that CMM was more prevalent in urban than in rural populations (4.8 in urban men and 5.2 in urban women vs 3.2 and 3.8 in rural men and women, respectively). Thus, CMM incidence increased with population density, a finding that does not agree with the UV radiation hypothesis. Since these discrepancies might be explained by the fact that foreign travel (ie, sunshine trips) among the city dwellers would expose them to more sunlight, a regression analysis of the epidemiological index for UV irradiation and melanoma incidence, adjusted for frequency of foreign travel was carried out. This analysis demonstrated a positive correlation between passport issue frequency, regional latitude, and melanoma incidence (coefficient of 0.83). There was good agreement between the slope of the regression line for latitude and that for the epidemiologic index (coefficient of -0.15). (40 refs)

79-1499 Recommendations of the International Commission of Radiation Protection, 1977. (Fre) Stewart, C. G. (Chalk River Nuclear Labs., Atomic Energy Canada Ltd., Chalk River, Ontario, Canada). *Radioprotection* 13(4): 237-247; 1978.

The 1977 recommendations of the International Commission on Radiation Protection (ICRP) are presented. The cancer risk of ionizing radiation is estimated (in Sieverts per yr) at 2×10^{-3} for the lungs and red marrow, 2.5×10^{-3} for the breast, 4×10^{-3} for the gonads, 5×10^{-4} for the thyroid and bones, and 5×10^{-3} for other tissues. For any organ or any combination of organs, the annual dose should not exceed 5 rem (roentgen-equivalents-man). (16 refs)

79-1500 Double Strand-Breaks and DNA-to-Protein Cross-Links Induced by Fast Neutrons in Bacteriophage DNA. (Eng) Hawkins, R. B. (Dept. Anatomy and Neurobiology, Washington Univ. Sch. Medicine, St. Louis, MO, 63110). *Int J Radiat Biol* 35(1): 1-13; 1979.

Coliphage T7 was suspended in tryptone broth and exposed to a mixture of fast neutrons and gamma radiation. Plaque survival, double-strand breaks, and DNA-protein cross-links were examined. Inactivation of plaque-forming activity appeared to be exponential at the rate of 5.6×10^{-6} inactivation/rad of the mixed neutron-gamma radiation/phage. Thus, the rate of inactivation from neutrons was calculated to be 3.5×10^{-6} /rad of neutron radiation/phage. The pattern of neutral sucrose gradient sedimentation in neutron-gamma-irradiated phage was bimodal, showing an accumulation of small DNA fragments near the top of the gradient with increasing dose. The pattern for phage exposed to gamma radiation alone was not bimodal. Neutrons appeared to cause two types of events in the T7 virion, one involving the deposi-

tion of a large amount of energy in the phage and one involving the deposition of a smaller amount of energy. With the former, 100 or more double-strand breaks were formed per event, whereas with the latter, zero or only a few breaks occurred. Neutron-induced protein-DNA cross-links probably also occur in clusters with enhanced efficiency being relative to low-LET (linear energy transfer) radiation. (17 refs)

- 79-1501 Effect of Destruction of Hypophysis by Radiation on Chemically Induced Mammary Gland Carcinoma in Rats.** (Rus) Savinskaia, A. P. (Cancer Res. Center, Moscow, USSR); Minakova, E. I. *Med Radiol (Mosk)* 24(2): 53-57; 1979.

The effect of radiation-induced destruction of the hypophysis on mammary gland carcinogenesis was studied in 48 albino random-bred rats. Animals received a single po dose of 7,12-dimethylbenz(a)anthracene (DMBA: 20 mg in 0.5 ml of peach oil). Six months later (at this time, all rats were free of mammary gland tumors), 24 rats underwent a single irradiation of the hypophysis with a proton beam (15,000-30,000 rads); 24 rats served as nonirradiated controls. Animals were sacrificed within 5 mo of irradiation, and mammary glands were examined macroscopically and total sagittal sections of the head were examined histologically. Only 1/24 irradiated rats developed a mammary gland adenocarcinoma vs 18% of the nonirradiated rats. There was no association between degree of destruction of the hypophyseal tissue and tumor incidence (the rat with the adenocarcinoma had a completely preserved hypophysis, while another rat with a completely destroyed hypophysis had hyperplasia of the mammary glands). (25 refs)

- 79-1502 Secondary Malignant Neoplasms Following Radiotherapy of a Mouse Mammary Carcinoma.** (Eng) Urano, M. (Dept. Radiation Medicine, Massachusetts General Hosp., Boston, MA, 02114); Koike, S.; Ohara, K. *Cancer* 43(1): 151-156; 1979.

The occurrence of secondary malignant neoplasms (SMN's) following radiotherapy of malignant neoplasms was studied using an animal tumor system, and clinical studies of SMN's following radiotherapy of malignant tumors were surveyed. The experimental tumors were third-generation isografts of a mammary carcinoma that arose spontaneously in a C3Hf/He mouse. Application of a single radiation dose ranging from the TCD20 to the TCD98 (radiation dose that yields a 20%-98% probability of local tumor control in 150 days; 5,200, 5,500, 5,900, or 6,300 rads were used) was followed by weekly observations. Most recurrences were observed in the first 150 days, and only a few were seen in the subsequent 150 days. Secondary neoplasms developed frequently following this period, ie, 41/67 animals surviving > 300 days developed secondary neoplasms. They were osteogenic and soft tissue sarcomas, and half the new tumors were found within 490 days after radiotherapy. The results were compared with literature reports of SMN's postoperative ra-

diotherapy for carcinoma of the breast and treatment of retinoblastomas. Most of these secondary human neoplasms were nonepithelial sarcomas. There are a few reports of the occurrence of secondary carcinomas following radiotherapy for carcinoma in other locations, such as the cervix and the head and neck. (38 refs)

- 79-1503 Hyperthermia and Radiation Induced Genetic Aberrations in *Drosophila melanogaster*.** (Eng) Mittler, S. (Dept. Biological Sciences, Northern Illinois Univ., DeKalb, IL, 60115). *Mutat Res* 59(1): 123-128; 1979.

Experiments were carried out in *Drosophila melanogaster* to determine whether hyperthermia could act as a sensitizer for the induction of dominant lethals, recessive lethals and chromosome loss, and nondisjunction by radiation. The number of eggs that hatched following fertilization by males exposed to heat alone (38 C, 1 hr) was unaffected by the heat treatment. However, the number of dominant lethals was increased significantly by subjecting males to heat treatment before or after irradiation (1,000 R), compared with the number induced by irradiation alone. The percentage of dominant lethals was particularly high (83.7%-83.8%) when males were exposed to irradiation and hyperthermia during meiosis I (6- to 8-day brood). Hyperthermia also significantly increased the percentage of radiation-induced recessive sex-linked lethals in three broods (0-2, 2-4, and 4-6 days). Irradiation followed by hyperthermia produced a slight increase in nondisjunction. However, when hyperthermia was applied before irradiation, significant losses of X and Y chromosomes were induced in broods 4-6, 2-4, and 6-8 days. Hyperthermia may cause sensitization to radiation by interfering with repair processes. (14 refs)

- 79-1504 The Induction of Gamma-Endonuclease-susceptible Sites by γ -Rays in CHO Cells and Their Cellular Repair Are Not Affected by the Presence of Thiol Compounds During Irradiation.** (Eng) Van Der Schans, G. P. (Medical-Biological Lab. TNO, Lange Kleiweg 139, 2280 AA Rijswijk Z.H., Netherlands); Centen, H. B.; Lohman, P. H. *Mutat Res* 59(1): 119-122; 1979.

An enzymic assay was used to monitor the disappearance of base damage from Chinese hamster ovary cells following γ irradiation in order to determine whether the ratio of endonuclease-susceptible sites to single-strand breaks could be made higher by the presence of 20 mM cysteamine (CA) during irradiation. DNA was extracted from ^3H -labeled, CA-treated, irradiated cultures at different times after irradiation, incubated with or without a crude cell-free extract of *Micrococcus luteus*, and centrifuged through alkaline sucrose gradients, which were then fractionated. The radioactivity profiles obtained by counting the fractions were subsequently analyzed by computer. From the profiles obtained after treatment with and without the extract, the number of single-strand DNA scissions introduced by γ -specific endonuclease could be determined. CA protected well against γ -

ray-induced single-strand breaks and alkali-labile sites, whereas it did not influence significantly the number of endonuclease-susceptible sites. The rate of repair of endonuclease-susceptible sites was not significantly different for irradiation in the absence or presence of 20 mM CA or 20 mM cysteine. The application of CA during irradiation may aid in the elucidation of different repair processes in human cells. (8 refs)

79-1505 Radiation Exposures of Hanford Workers Dying from Cancer and Other Causes (Letter to Editor). (Eng) Kneale, G. W. (Regional Cancer Registry, Queen Elizabeth Medical Centre, Birmingham B15 2TH, England); Stewart, A. M.; Mancuso, T. F. *Health Phys* 36(1): 87; 1979.

It was not claimed, as previously misunderstood, that cancer was a major hazard of the nuclear industry or that the cancer mortality of Hanford nuclear plant workers was significantly raised, but rather that there is prima facie evidence of a relationship between cancer mortality from certain specific cancers and radiation, even at the low doses received by Hanford workers. This conclusion was confirmed by two additional groups of scientists with access to the same data. They have implicated two of the three cancers named as showing a dose-response relationship (pancreatic cancer and multiple myeloma). (no refs)

79-1506 Cell Survival Following Multiple-Track Alpha Particle Irradiation. (Eng) Lloyd, E. L. (Center Human Radiobiology, Argonne Natl. Lab., Argonne, IL, 60439); Gemmell, M. A.; Henning, C. B.; Gemmell, D. S.; Zabransky, B. J. *Int J Radiat Biol* 35(1): 23-31; 1979.

The survival of mouse embryo fibroblasts (C3H 10T1/2, clone 8) following irradiation with a parallel beam of alpha particles from a Tandem Van de Graaff generator was studied. When plated on plastic Petri dishes, the cells quickly assumed a flattened appearance, and the nuclear area increased from approx 100 to 313 μm^2 . The mean lethal radiation dose for these cells was about 60 rads and an av of 14 alpha particles passed through the nucleus to produce this mean lethal dose. This finding suggests that cells that are similarly flattened against bone surfaces in the body might survive multiple traversals of alpha particles and give rise to malignancies at later times. (16 refs)

79-1507 Low-Intensity Microwave Radiation and the Virulence of *Agrobacterium tumefaciens* Strain B6. (Eng) Moore, H. A. (Dept. Physics, Bradley Univ., Peoria, IL, 61525); Raymond, R.; Fox, M.; Galsky, A. G. *Appl Environ Microbiol* 37(1): 127-130; 1979.

The effects of low-level microwave radiation (10,000 megahertz at 0.58 milliwatt/cm² for 30-120 min) on the virulence

of *Agrobacterium tumefaciens* strain B6 were studied. Exposure of *A. tumefaciens* to microwave radiation resulted in a 30%-60% decrease in their ability to produce tumors on potato and turnip disks. Irradiation resulted in no loss of viability, and there was no loss of virulence or viability when the cells were wrapped in aluminum foil prior to irradiation. The loss in virulence of the unwrapped irradiated cells was not due to an inability to compete for tumor-binding sites or to any major thermal effects. Complete virulence was restored 12 hr after exposure to microwave radiation, although storage at 4 C slowed the restoration to full virulence. It is possible that microwave exposure temporarily alters one or more metabolic processes affecting virulence. (13 refs)

79-1508 Cholangiocarcinoma and Hepatosplenic Atrophy Subsequent to Thorotrast Administration. (Ita) Caresano, A. (Servizio di Radiologia, Ospedale di Circolo, 57 viale Borri, I-21100 Varese, Italy); Conte, L.; Curzio, M.; Provasi, A.; Del Favero, C.; Nanni, R. *Radiol Med (Torino)* 64(11): 1267-1273; 1978.

A woman underwent cerebral angiography with iv Thorotrast (TT). She developed jaundice and died in coma 38 yr later, at the age of 54. Radioactivity was found in the spleen, liver, and lymph nodes. Autopsy revealed a cholangiocarcinoma and atrophy of the liver, spleen, and lymph nodes. The TT dose was estimated to have been 3,000 rads. The high radiation dose and the time lapse justify the hypothesis that the neoplasm was caused by TT. (21 refs)

79-1509 Photodynamic Effects of Dyes on Bacteria. II. Genetic Effects of Broad-Spectrum Visible Light in the Presence of Acridine Dyes and Methylene Blue in Chemostat Cultures of *Escherichia coli*. (Eng) Webb, R. B. (Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL); Hass, B. S.; Kubitschek, H. E. *Mutat Res* 59(1): 1-13; 1979.

Photodynamic mutagenesis was studied in chemostat cultures of *Escherichia coli* B/r (T1-R *trp*) exposed to one of six acridine dyes of methylene blue (MB). Mutation to phage T5 resistance was induced with a broad-spectrum fluorescent light source. In the presence of light, acridine yellow (AY) was the most effective sensitizing agent for mutagenesis, and quinacrine hydrochloride (Q) the least effective. There was no detectable lethality for any combination of dye concentration and light fluence rate. There was no observable correlation between dye-induced mutation rates in the presence and absence of light; Q gave the largest dark mutation rate. Acridine orange (AO), proflavine (P), and MB mutation rates were proportional to fluence rate and also to dye concentration. Rates of photomutagenesis with AO, MB, or P were independent of growth rate in continuous cultures. The mean-delay period for expression of mutation to phage T5 resistance was also independent of growth rate, the values for various dyes being consistent with an expression delay of 2.5 generations. High concentrations of putrescine or spermidine

did not reduce the rate of AO/light or P/light mutagenesis. The photomutagenic actions of AO and acridine were not additive. The results suggest that photodynamic mutagenesis is due mainly to intercalated dye molecules. (38 refs)

- 79-1510 Increased Susceptibility of Mouse Cells to Fluorescent Light-induced Chromosome Damage After Long-Term Culture and Malignant Transformation.** (Eng) Parshad, R. (Dept. Pathology, Howard Univ. Coll. Medicine, Washington, DC, 20059); Sanford, K. K.; Tarone, R. E.; Jones, G. M.; Baeck, A. E. *Cancer Res* 39(3): 929-933; 1979.

The effects of prolonged time in culture and spontaneous malignant transformation on fluorescent light-induced chromosome damage were studied in mouse NCTC cells. The light-exposed cells showed significant increases in chromatid breaks and chromatid exchanges, and the frequency of meta-centric chromosomes in both shielded and exposed cells increased with time in culture. Increased susceptibility to light-induced chromatid breaks and exchanges occurred in cultures after about 400 days in vitro. Cells from older cultures inoculated into syngeneic hosts grew as sarcomas. In most shielded cultures, the frequency of chromatid breaks and exchanges did not increase with time in culture. Cells of three lines showed a significantly increased susceptibility to both chromatid breaks and exchanges after spontaneous transformation. One cloned line that was unusually resistant to spontaneous transformation was also resistant to light-induced chromosome damage, as was its malignant derivative. The frequency of light-induced chromatid breaks was lower in the nonneoplastic clone than in other mouse cells, although the frequency of light-induced breaks was higher in the malignant derivative than in the nonneoplastic parent clone. Increased susceptibility to light-induced chromatid damage could result from impaired DNA repair or from the loss of defence mechanisms for destroying H_2O_2 or scavenging free radicals. (17 refs)

- 79-1511 Radioactivity in Asbestos.** (Eng) Harley, N. H. (Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY); Cohen, B. S.; Pasternack, B. S.; Fisenne, I. M.; Rohl, A. N. *Environ Int* 1(4): 161-165; 1978.

Total alpha activity and ^{226}Ra activity were measured in five types of asbestos. The ^{226}Ra values varied considerably, with California chrysotile having the lowest value [≤ 0.009 picocuries (pCi)/g] and amosite from the Unarco plant having the highest value (0.35 pCi/g). The total alpha activity varied from 0 [Union Internationale Contre le Cancer (UICC) Cape Blue crocidolite] to 1.4 pCi/g (Unarco amosite). The total alpha activity of the UICC standard amosite and crocidolite (Cape Blue and Transvaal Blue) samples appeared to be lower than that of the same three samples obtained as impure ores. Alpha particles from asbestos fibers immobilized in the lower lung near the pleural surfaces and in the upper lung on bron-

chial surfaces may be implicated in initiating mesothelioma and bronchial carcinoma. (27 refs)

- 79-1512 Kinetics of Intracardially Injected Plutonium-237 Citrate in Channel Catfish (*Ictalurus punctatus*).** (Eng) Trabalka, J. R. (Environmental Sciences Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Eyman, L. D.; Frank, M. L.; Bergman, H. L. *Health Phys* 35(6): 779-784; 1978.

Plutonium-237 (^{237}Pu) distribution and translocation were studied in channel catfish (*Ictalurus punctatus*) following intracardial injection of ^{237}Pu citrate (0.075 ml of 1 μCi $^{237}Pu/cm^3$ saline soln). Fish were sacrificed at 1, 2, 3, 10, and 17 days after injection. Plasma contained 90% or more of the blood-associated ^{237}Pu . Within the plasma from a control fish spiked with ^{237}Pu and incubated at 3 C for 24 hr, 72% of the Pu was contained in one fraction, the iron-binding globulin transferrin. The fractional body burdens in bone, liver, and kidney 17 days after injection were 31%, 24%, and 9% of the injected dose, respectively. High kidney burdens relative to mammals were expected, since the kidney functions as the major site of hemopoiesis in teleosts. Five of the 10 ovaries sampled contained ^{237}Pu concentrations comparable to liver values, but the remaining 5 ovaries carried concentrations similar to those in bone and gill. Muscle and skin contained 31% of the body burden on day 1, but this value fell to 16.6% on day 17. Excretion over the 17-day period was $\leq 10\%$. The absence of significant excretion indicates that a short half-life component of elimination following gut clearance in earlier gavage studies is due to Pu labeling of the gut. The results suggest that assimilated Pu should be insignificant in aquatic food chain transfers. (24 refs)

- 79-1513 Carcinogenicity of Inhaled Air-oxidized $^{239}PuO_2$ in Rats.** (Eng) Sanders, C. L. (Dept. Biology, Pacific Northwest Lab., Richland, WA, 99352); Mahaffey, J. A. *Int J Radiat Biol* 35(1): 95-98; 1979.

The metabolism and carcinogenicity of inhaled air-oxidized (AO) $^{239}PuO_2$ were studied in random-bred female specific-pathogen-free Wistar rats, and the results were compared with those obtained previously using high-fired (HF) $^{239}PuO_2$. The animals were exposed for 30 min at 70 days of age. During the first few weeks after exposure, HF and AO particles were scattered throughout the lung parenchyma. All the alpha tracks for HF and 90% of those for AO $^{239}PuO_2$ that were deposited in the lung were in the form of stars. About 40% of the initial alveolar deposition (IAD) of the HF particles and about 28% of that of the AO particles remained in the lung 30 days after exposure. More AO than HF $^{239}PuO_2$ was translocated from the lung into the liver and skeleton. Four HF-exposed rats exhibited two different types of primary lung tumor, whereas none of the AO-exposed rats exhibited more than one lung tumor. The primary lung tumors produced, in decreasing order of frequency, were adenocarcinoma, squamous cell carcinoma, hemangiosarcoma, meso-

thelioma, and fibrosarcoma. The incidence of lung tumors in AO- and HF-exposed rats was significantly increased over control values. However, lung tumor incidence with an AO IAD of 9.9 nanocuries (nCi) was significantly greater than that with an HF IAD of 5.5 nCi (28% vs 10%), but not significantly less than that with an HF IAD of 45 nCi (37.4%). This suggests that AO $^{239}\text{PuO}_2$ was more efficient in inducing lung tumors than HF $^{239}\text{PuO}_2$, possibly due to a more uniform exposure of lung cells with the former. (6 refs)

79-1514 Influence of the Mass of Administered Plutonium on Its Cross-placental Transfer in Mice.

(Eng) Weiss, J. F. (Comparative Animal Res. Lab., 1299 Bethel Valley Road, Oak Ridge, TN, 37830); Walburg, H. E. *Health Phys* 35(6): 773-777; 1978.

The mass effect for placental transport of plutonium (Pu) was studied in BALB/c mice. Pregnant mice were injected in the tail vein with one of three doses of $^{239}\text{Pu(IV)}$ citrate 16 days after mating (0.098, 2.38, or 26.91 $\mu\text{Ci/kg}$ in one experiment and 0.10, 2.41, and 26.56 $\mu\text{Ci/kg}$ in another). The mice were killed and tissues prepared for analysis 48 hr after injection. There was an inverse relationship between mass of Pu administered and amount transferred to the fetuses, placentas, and maternal tissues. No significant differences in percentage of dose incorporated were observed in similar tissues between the two lower dose levels (av values of both experiments combined): fetus, 4.76% and 4.37%; placenta, 15.75% and 14.60%; maternal femur, 1.47% and 1.51%; and remainder of maternal carcass, 59.82% and 63.51%. The highest dose level showed a significantly reduced percentage of dose incorporated into fetus (1.29%), placenta (7.09%), and maternal femur (0.76%). There was a significantly higher percentage of incorporation in the remainder of the carcass at the highest dose (72.67%). These data indicate that estimates of cross-placental transfer of Pu and fetal uptake at low dose levels derived from observations at high doses are likely to be in error. (13 refs)

79-1515 Calculated MPC-a Values for $^{239}\text{PuO}_2$ By Comparing the Added Risk of Cancer with the Accepted Occupational Risks.

(Eng) De Bont, A. H. (Dept. Health Physics, Univ. Nijmegen Toernooiveld Nijmegen, Holland 6525 ED); Beentjes, L. B. *Health Phys* 36(1): 53-58; 1979.

Values of the max permissible concentration in air (MPC-a) of $^{239}\text{PuO}_2$ were calculated by comparing the added risk of cancer with the accepted occupational risks. Specifically, the risks of cancer induction in bone, lungs, liver, and tracheo-bronchial lymph nodes was considered. Two deposition and distribution models were used: the New Lung model (NLM) and a modification of this model (NLMP) that corrects for the effect of particle size on the rate of removal of radioactive material from the lungs. It was assumed that MPC-a should be chosen such that the risk incurred by exposure for 40 hr/wk over 50 yr would still be acceptable; $1 \times 10^{-4}/\text{yr}$ was

taken as an acceptable risk rate. When the NLM was used, the lung was the organ subject to the highest cancer induction risk. When the NLMP was used, the lung was again the critical organ, especially with particle sizes $\geq 1 \mu\text{m}$ activity median aerodynamic diameter (AMAD); the liver was the critical organ with particle sizes of 0.1-0.01 μm AMAD. The possibility that at small doses cancer induction risk may not be linearly related to dose was not considered. Limitation of the cancer induction risk rate to $1 \times 10^{-4}/\text{yr}$ implies a reduction of the max permissible dose equivalent for the total body by a factor of 6. (12 refs)

79-1516 ^{90}Sr in Placentas, Embryos and Foetuses of Mice, Evaluated by Whole-Body Autoradiography.

(Eng) Olsen, I. (Dept. Microbiology, Dental Faculty, Univ. Oslo, Blindern, Oslo 3, Norway); Jonsen, J. *Acta Pharmacol Toxicol (Kbh)* 44(1): 22-27; 1979.

Whole-body autoradiography was used to study the fetal uptake and retention of ^{90}Sr (single dose of 50 μCi , given ip within days 5-18 of gestation) and the embryonic transfer of this isotope as a function of gestational age. The pregnant dams were killed 15 min to 72 hr after injection. ^{90}Sr was found in the visceral yolk sac and chorioallantoic placenta 15 min after injection on gestation day 14. These concentrations declined by 24 hr after injection and were not detectable at 72 hr. ^{90}Sr was first seen in the 14-day-old fetus 4 hr after injection; the concentrations in the soft tissues peaked at 12 hr and were not detectable at 72 hr, whereas those in the hard tissues continued to increase. ^{90}Sr passed the placental barriers throughout gestation, being found in all fetuses and the visceral yolk sac on days 5-18. The isotope did not appear in the chorioallantoic yolk sac until day 11. ^{90}Sr gradually accumulated in preskeletal and skeletal tissues, the distribution becoming more differentiated and more like that of the mother with increasing gestational age. Intake of ^{90}Sr during early gestation may be more injurious to the offspring than intake during late gestation. (21 refs)

79-1517 Solvent Extraction Method for Determination of Thorium in Soft Tissues.

(Eng) Singh, N. P. (Inst. Environmental Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016); Ibrahim, S. A.; Cohen, N.; Wrenn, M. E. *Anal Chem* 51(2): 207-210; 1979.

A method for the determination of thorium isotopes in soft tissues consists of preliminary nitric acid digestion of tissues after adding ^{229}Th tracer followed by digestion with a mixture of nitric and sulfuric acid plus occasional addition of a few drops of H_2O_2 ; thorium is then coprecipitated with iron carrier by ammonium hydroxide. The compound is extracted into trilaurylamine + xylene and determined by α spectrometry with a surface-barrier silicon detector. Final total recovery ranged from 24%-93% with a mean of 65% in 28 samples. (10 refs)

- 79-1518 Osteosarcoma Associated with Thorotrast Administration: Report of Two Cases and Literature Review.** (Eng) Sindelar, W. F. (Surgery Branch, NCI, NIH, Bethesda, MD, 20014); Costa, J.; Ketcham, A. S. *Cancer* 42(6): 2604-2609; 1978.

The occurrence of osteosarcoma in two patients who had undergone angiography with Thorotrast in childhood is reported, and similar cases in the literature are reviewed. In both patients, there was radiographic and pathologic evidence of thorium dioxide deposition in bone and throughout the reticuloendothelial system. Thorotrast deposits were demonstrated in the immediate vicinity of the primary tumors by both histologic and autoradiographic studies. (21 refs)

- 79-1519 Effect of Receiver Orientation on Erythema Dose.** (Eng) Burt, J. E. (Dept. Geography, Univ. California, Los Angeles, CA, 90024); Luther, F. M. *Photochem Photobiol* 29(1): 85-91; 1979.

The significance of receiver orientation (inclination angle and azimuth angle) to the solar flux dose received in the wavelength region responsible for erythema (sunburn) and skin cancer was determined. A semiempirical model was used to calculate erythema dose for nonhorizontal plane areas under cloudless conditions as a function of latitude, season, and ozone amount. According to the model, in middle and high latitudes, surfaces with inclination angles (α) up to 45 degrees receive at least 80% of the daily erythema dose received by a horizontal surface. Much larger reductions in daily erythema dose occur for $\alpha > 45$ degrees, which can result in a significant reduction in the latitudinal gradient of erythema dose. The amplification factor for erythema dose ($\Delta\text{dose}/\Delta O_3$) varies significantly with latitude, but it is only weakly dependent upon receiver orientation. Additional calculations indicate that the amplification factor may be significantly larger for skin cancer than for erythema. (31 refs)

- 79-1520 Alpha Irradiation of the Skin and the Possibility of Late Effects.** (Eng) Sevcova, M. (Dept. Dermatology, Health Inst. Uranium Industry, 261 00 Pribram, Czechoslovakia); Sevc, J.; Thomas, J. *Health Phys* 35(6): 803-806; 1978.

Exposure of uranium miners to alpha radiation is important because of contamination of the skin surface by radon (^{222}Rn) daughters. Based on data on epidermal thickness, which is less than 50 μm or 5 mg/cm^2 on the face and trunk in 50% of humans, an estimate was made of the dose equivalent delivered to the basal layer of the epidermis. In Czechoslovak uranium miners working 1,700 hr/yr, the mean dose equivalent in the basal layer of the epidermis will be 60 rem (roentgen-equivalent-man)/yr. In persons having a thin epidermis, the dose equivalent will be two times higher. Before the initiation of current standards, the concentration of radon daughters in uranium mines exceeded the current permissible value by approx 10 times, allowing the cumulative dose equivalent

to reach several thousands of rem following an exposure of many years duration. In a group of several thousand uranium miners, the incidence of skin cancer (mainly basal cell carcinoma) during 1968-1975 was significantly higher than expected, particularly among miners with > 10 yr exposure. These results indicate the possibility of a carcinogenic effect of external alpha irradiation of the skin. (12 refs)

- 79-1521 Giant Cell Tumor after Exposure to Cobalt-containing Dust: Cobaltous Phthalocyanine (Merox Catalyst).** (Ger) Schulz, G. (Arbeitsmedizin Ltd., Dtsch. B.P. A.G., Mexikoring 23, 2000 Hamburg 60, W. Germany). *Staub-Reinhalt Luft* 38(12): 480-481; 1978.

A 49-yr-old oil refinery worker developed a fast-growing giant cell tumor in his cheek 5 mo after his oral and buccal membranes were accidentally exposed to dust containing cobaltous phthalocyanine, a mercox catalyst. The recurring tumor was a foreign body granuloma that contained Langhans giant cells and cobalt salts. (7 refs)

- 79-1522 Differentiated Thyroid Cancer Following Radioiodine ^{131}I Therapy of Hyperthyroidism--A Case Report.** (Eng) Nemec, J. (Res. Inst. Endocrinology, 115 94 Prague, Czechoslovakia); Soumar, J.; Zeman, V.; Nahodil, V.; Zamrazil, V.; Smejkal, V. *Oncology* 35(6): 277-280; 1978.

The case of a 65-yr-old man who developed differentiated (papillary) thyroid cancer 17 yr after ^{131}I treatment for toxic multinodular goiter is presented, and 21 similar literature cases are summarized. The paucity of ^{131}I -associated thyroid cancers in comparison with those associated with external radiation may be due to differences in absorbed dose. (26 refs)

- 79-1523 Development of Carcinoma of the Breast at the Site of an Implanted Pacemaker in Two Patients.** (Eng) Biran, S. (Dept. Oncology, Hadassah Univ. Hosp., Jerusalem, Israel); Keren, A.; Farkas, T.; Stern, S. *J Surg Oncol* 11(1): 7-11; 1979.

Two women who had permanent pacemakers (PM's) implanted in their chests subsequently developed breast carcinoma. Patient 1 (64 yr old) had undergone a left radical mastectomy + radiation therapy in 1953 because of carcinoma simplex of the breast. A PM was implanted into the right subclavicular area in 1975 because of alternating second- or third-degree block with junctional rhythm. In 1977, a firm mass was noted in the patient's right breast, slightly below the PM box. The biopsy result was positive for intraductal-type carcinoma. Patient 2 (65 yr old) had a PM implanted for complete atrioventricular block in the subclavicular area of the right chest, bordering the right breast. Several months later, a discharge from the nipple of her right breast was noted. Subsequent physical exam revealed a mass slightly above the nipple and two enlarged lymph glands in the right

axilla. Biopsy 18 mo after PM implantation showed adenocarcinoma and Paget's disease. Because a connection between mammary carcinoma and the PM is suspected, the site of the sc pocket for implanting the PM in female patients was changed to a position higher in the chest, to avoid contact between the PM and the mammary tissue. (14 refs)

- 79-1524 Induction of Pulmonary Carcinoma in Rats by Chronic Inhalation of Dust from Pulverized Asbestos Pipe Covering.** (Eng) Leong, B. K. (International Res. and Development Corporation, 500 N. Main St., Mattawan, MI, 49071); Kociba, R. J.; Pernell, H. C.; Lisowe, R. W.; Rampey, L. W. *J Toxicol Environ Health* 4(4): 645-659; 1978.

Fifty male Sprague-Dawley rats and 15 male golden hamsters were exposed to dust generated by pulverization of prefabricated asbestos pipe covering (PAPC) and observed for subsequent development of pulmonary disease. Animals were exposed to dusts containing 0.5- to 10.5- μ m particles (mean diameter, 4.1 μ m) and very few fibers at a concentration of 85 mg/m³ for 6 hr/day, 5 days/wk, over 7 mo (150 total exposures). Five experimental and five control rats were sacrificed at the end of exposure or at 1, 6, and 18 mo postexposure (PE). Otherwise animals were allowed to die naturally. The mean body wts of the rats were significantly lower than those of controls until 14 mo PE, but there was no difference in mortality between the groups. Up to 6 mo PE, pulmonary deposits of dust were visible grossly as isolated subpleural pale foci, and isolated aggregates of dust-laden macrophages were visible microscopically within alveoli. However, there were no marked accumulations of intraalveolar proteinaceous material, WBC, inflammatory debris, or fibrogenic responses. At 14-29 mo PE, there were instances of alveolar hyperplasia, alveolar adenomatous proliferation, nonprogressive fibrosis, and squamous metaplasia of alveoli. Moreover, 6/34 rats had pulmonary carcinomas compared with 0/35 controls. Eight hamsters died early during the exposure period, two with pulmonary lesions. In the seven surviving animals, all of which died within 17 mo, there were isolated aggregates of particle-laden macrophages, and three hamsters displayed minimal focal alveolar epithelial hyperplasia. None of the hamsters developed tumors. The dust used is the type to which pipe insulation workers may be exposed. (24 refs)

- 79-1525 Thorotrastosis--Viewed in Retrospect.** (Ger) Autenrieth, J. (Strahlenklinik, Freie Universitat Berlin im Klinikum Charlottenburg, Spandauer Damm 130, 1000 Berlin 19, W. Germany); Lange, S. *Roentgenblaetter* 32(2): 71-74; 1979.

Two tumors attributable to the diagnostic use of Thorotrast (TT) are reported and the literature on thorotrastosis is reviewed. A 61-yr-old woman developed hepatocellular carcinoma plus fibrosis and atrophy of the spleen 29 yr after TT angiography of the cerebral vessels. Another woman developed a foreign-body granuloma of the thigh several years after TT angiography of the pelvic and femoral region. Typi-

cal TT deposits were found in the liver, spleen, and perigastric lymph nodes. (14 refs)

- 79-1526 Thorotrast Induced Hepatic Cholangiocarcinoma and Angiosarcoma.** (Eng) Winberg, C. D. (Dept. Pathology, Stanford Univ. Sch. Medicine, Stanford, CA); Ranchod, M. *Hum Pathol* 10(1): 108-112; 1979.

A 49-yr-old woman developed hepatic cholangiocarcinoma and angiosarcoma 22 yr after the administration of Thorotrast (TT: colloidal thorium dioxide) for cerebral arteriography. Abdominal roentgenograms revealed regions of very high density in the liver and spleen that were interpreted as residual TT. TT granules were found in a liver biopsy specimen. This is the first report of the simultaneous occurrence of two different hepatic tumors in association with TT exposure. (21 refs)

- 79-1527 Thorotrast Associated Hepatic Angiosarcoma with 36 Years Latency.** (Eng) Underwood, J. C. (Dept. Pathology, Univ. Sheffield Medical Sch., Beech Hill Road, Sheffield S10 2RX, England); Huck, P. *Cancer* 42(6): 2610-2612; 1978.

Radiological and autoradiographic findings in a case of hepatic angiosarcoma that developed 36 yr after thorotrast administration are reported. The patient had received a total of 23 ml of the agent at the age of 9. A needle liver biopsy, examined 3 mo before death, showed a spindle cell vascular neoplasm insinuating between liver cells. Autoradiography demonstrated that the neoplasm was associated with granular thorium deposits. (7 refs)

- 79-1528 Haemangioendothelioma (Kupffer Cell Angiosarcoma), Myelofibrosis, Splenic Atrophy, and Myeloma Paraproteinaemia After Parenteral Thorotrast Administration.** (Eng) Jennings, R. C. (Altrincham General Hosp., Cheshire, England); Priestley, S. E. *J Clin Pathol* 31(12): 1125-1132; 1978.

The case report of a 74-yr-old woman with Thorotrast (TT: thorium dioxide suspension)-induced multifocal hepatic hemangioendothelioma (Kupffer cell angiosarcoma), splenic atrophy, myelofibrosis, and myeloma-type paraproteinemia is presented. In 1952, 25 yr prior to the diagnosis, she had been given 45 ml TT parenterally for a carotid angiogram. Histologically, the liver showed prominent TT pigment deposition, mainly in the portal tracts and to a lesser extent scattered throughout the parenchyma with a variable amount of intervening normal hepatic tissue. Multiple blood-containing cysts were present that, at their inception, were lined by a single layer of phagocytic tumor cells; as they enlarged, they revealed both solid and papillary intracystic tumor cell groups. The spleen showed pronounced pigment deposition. Between the large focal groups of pigment granules, there was a fibrosing cellular parenchyma with some necrosis but virtu-

ally no residual normal splenic tissue. Bony myelomatous deposits together with paraproteinemia were also found. The parietal bone showed two hemorrhagic cystic lesions with plasma cell groups within the cystic spaces. The bone marrow from the sternum and iliac crest showed some pigment deposition with alternating areas of hyperplasia and myelofibrosis and, in addition, focal aggregates of plasma cells. There was a diffuse chronic thyroiditis with reduction in colloid acinar production but with no pigment deposition. This is the first recorded association of TT angiography and myeloma-type paraproteinemia. The relationship between TT-induced hemangioendothelioma and other vascular sarcomas of the liver is reviewed briefly. (22 refs)

- 79-1529 Variation of Properties of Chrysotile Asbestos Subjected to Milling.** (Eng) Langer, A. M. (Environmental Sciences Lab., Dept. Community Medicine, Mount Sinai Sch. Medicine, City Univ. New York, Fifth Ave. and 100th St., New York, NY, 10029); Wolff, M. S.; Rohl, A. N.; Selikoff, I. J. *J Toxicol Environ Health* 4(1): 173-188; 1978.

Chrysotile asbestos samples were milled for 60-3,600 sec and then examined for alteration of surface or structural properties by electron microscopy, x-ray diffraction analysis, infrared spectroscopy, and electron spin resonance. The hemolytic activity and adsorption of diphenylpicrylhydrazyl (DPPH) to chrysotile were also investigated. The milling decreased fiber crystallinity, altered silicon-oxygen and magnesium-oxygen interlayer bonding, induced coordination changes in the brucite layer, diminished the ability of the fiber to reduce and physisorb DPPH, and decreased hemolytic potency and antagonist sorption capabilities. The degree of alteration was related to the duration of milling. The hypothesis that particle shape is the major etiologic mechanism in fibrotic or carcinogenic responses appears, in terms of these results, to be oversimplified, except insofar as morphology reflects more fundamental structural and surface physicochemical properties. Comparison of biological potentials of fibers of different lengths should take into account alterations of fiber characteristics by the preparation of various size fractions. (46 refs)

- 79-1530 Incidence of Gastric Cancer after Vagotomy and Pyloroplasty in the Rat.** (Eng) Junghanns, K. (Surgical Dept., Univ. Heidelberg, Heidelberg, W. Germany, Switzerland). *Chir Gastroenterol* 12(1): 27-29; 1978.

To study the effects of vagotomy and pyloroplasty on tumor induction, 1-methyl-3-nitro-1-nitrosoguanidine (MNG: 4 mg/day in the drinking water) was given to Wistar rats, some of which had undergone truncular vagotomy and pyloroplasty. Tumors developed in 93.5% of the operated rats after a mean dose of 1.8 g MNG and a median induction time of 430 days. Tumors developed in 75.5% of the control rats after a mean dose of 2.2 g MNG and a median induction time of 565 days. Most of the tumors were adenocarcinomas, and

they were most common in the glandular stomach and pylorus, especially in the operated rats; tumors of the duodenum and jejunum appeared more frequently in the controls. Both groups showed a large number of hepatic cysts. The operated and control groups did not differ statistically in terms of median induction time, mean dose of MNG, or tumor distribution. The data indicate that unlike gastric resection, vagotomy and pyloroplasty do not make the stomach more susceptible to the effects of exogenous carcinogens. (8 refs)

- 79-1531 Iodine-131 and Malignancy (Letter to Editor).** (Eng) Warner, T. F. (Dept. Pathology, Indiana Univ. Sch. Medicine, Indianapolis, IN, 46202). *Lancet* 1(8106): 38; 1979.

A multifocal adenocarcinoma of the proximal jejunum occurred in an 89-yr-old woman 18 yr after the ingestion of two 15-mCi doses of iodine-131 for toxic multinodular goiter. Widespread mucosal hyperplasia, dysplasia, and carcinoma in situ were present. Apart from three infiltrating tumors, three distinct histological types of adenocarcinoma were seen in other areas. These changes are suggested to be due to the ¹³¹I exposure. (5 refs)

- 79-1532 Induction of Bladder Carcinomas in Dogs.** (Eng) Gericke, D. (Hoechst AG, D-6230 Frankfurt, W. Germany); Harzmann, R.; Bichler, K. H.; Altenahr, E. *Naturwissenschaften* 65(12): 665-666; 1978.

The induction of experimental bladder carcinoma, using polymerizing plastic pellets with or without carcinogen treatment, was studied in four groups of dogs. The pellets were used to induce local irritation of the urothelium. In the first group, 1.5 ml of the fluid phase of the plastic methyl methacrylate were injected into the saline-filled urinary bladder. Polymerization occurred within 90-150 sec. In the second group, the plastic treatment was combined with o-aminodiphenyl treatment (30 mg/kg, twice weekly, sc). In the third group, plastic treatment was combined with 2-formylamino-4-(5-nitro-2-furyl)thiazole (FANFT) treatment (25 mg/kg, twice weekly, sc) and in the fourth group, it was combined with both carcinogens (20 mg/kg each, twice weekly). Carcinoma was diagnosed histologically between the 13th and 18th mo in 7/8 dogs in Groups 3 and 4. No animals in Groups 1 or 2 or in the control group showed invasive carcinoma or carcinoma in situ of the urothelium. (12 refs)

- 79-1533 Effects of Intraperitoneal Administration of Asbestos and Asbestos-Quartz Mixtures on Rats.** (Ger) Weller, W. (Silikose-Forschungsinstitut, Bergbau-Berufsgenossenschaft, Hunscheidtstrasse 12, D-4630, Bochum 1, W. Germany). *Int Arch Occup Environ Health* 42(3/4): 169-183; 1979.

The pathogenicity of chrysotile B (CT), crocidolite (CL), and quartz (QZ), alone and in combination, was studied in 197

1-yr-old female SPF Sprague-Dawley rats. Dusts of the minerals were suspended in physiological saline. When the substances were administered singly, the rats received 5, 10, or 15 mg in 1 ml saline ip. When they were administered in combination, the rats received 5, 10, or 15 mg QZ plus 15, 10, or 5 mg of either asbestos compound (each combination totaled 20 mg). Rats from each treatment group were sacrificed at 3 and 6 mo. Administration of QZ alone caused a dose-dependent increase in spleen and omentum wt; the other dusts and mixtures did not have this effect. The wts of the pulmonary lymph nodes and/or cranial mesenteric lymph nodes were clearly correlated to dust injections. The values were significantly higher with CL than with CT. With QZ + CL, the effects were additive; QZ + CT had an inhibitory effect. CL caused widespread adhesions in the omentum, spleen, liver, and diaphragm. CL alone or with QZ produced ascites and ovarian cysts. One or two mice in each experimental group (total, 12 mice) had sc fibroadenomas; these tumors were not seen in the controls. No asbestos fibers could be found in these tumors, and their significance is not clear. Fibrous (Grade III) granulomas were numerous in all CL groups; many asbestos fibers were seen at the highest dose. Ferruginous bodies were first noted at 6 mo in the group given the highest dose of CL. No signs of progression toward malignancy were seen in any of the lesions. (37 refs)

79-1534 Analysis of the Cores of Asbestos Bodies from the General Population: Correlation of Amphibole Subtypes and Sex (Meeting Abstract). (Eng) Churg, A. (Dept. Pathology, Univ. California, San Francisco, CA, 94143); Warnock, M. L. *Lab Invest* 40(2): 246-247; 1979. (no refs)

79-1535 Analysis of Asbestos Fibers in Various Alcoholic Beverages: Role of Contamination by Filtration Materials. (Fre) le Bouffant, L. (Centre d'études et recherches des Charbonnages de France, BP 2, 60550 Verneuil-en-Halatte, France). *Ann Nutr Aliment* 32(5): 1011-1019; 1978.

Samples of alcoholic beverages that had not been filtered or that had been filtered through asbestos were examined for the presence of asbestos fibers. The samples were filtered on a micropore membrane, and the membrane was examined un-

der an electron microscope. The fibers were identified by their morphology and x-ray diffraction pattern and, in some cases, by elemental microanalysis. All asbestos-filtered samples showed chrysotile fibers that generally occurred separately, although sometimes they were found in clumps. The unfiltered samples showed only small amounts of fibers, similar to the amounts found previously in water samples. (no refs)

79-1536 Use of Transmission Electron Microscopy for the Analysis of Chrysotile Asbestos in Wine. (Fre) Dufour, G. (Laboratoire d'étude des Particules Inhalées, Direction des Affaires Sanitaires et Sociales de Paris, 37 bd Saint-Marcel, 75013 Paris, France); Sebastien, P.; Gaudichet, A.; Bignon, J.; Bonnaud, G. *Ann Nutr Aliment* 32(5): 997-1009; 1978.

A method for analyzing chrysotile asbestos fibers in wines involves isolation of particles by microfiltration through a nucleopore membrane and entrapment of retained particles in a carbon layer. This layer is observed under a transmission electron microscope fitted with an x-ray-scattering spectrometer. Chrysotile fibers are identified on the basis of morphology, elemental composition, and crystal structure. (29 refs)

See also:

*(Rev.): 79-1233, 79-1234, 79-1236, 79-1237, 79-1238, 79-1239, 79-1240, 79-1241, 79-1242, 79-1243, 79-1244, 79-1245, 79-1246, 79-1247, 79-1272, 79-1290.

*(Chem.): 79-1308, 79-1323, 79-1354, 79-1397.

*(Viral): 79-1629, 79-1638.

*(Path.): 79-1703, 79-1711.

*(Epid.-Biom.): 79-1741, 79-1742, 79-1743, 79-1777.

VIRAL CARCINOGENESIS

- 79-1537** **Defectiveness of Avian Erythroblastosis Virus: Synthesis of a 75K gag-related Protein.** (Eng) Hayman, M. J. (Dept. Tumour Virology, Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Royer-Pokora, B.; Graf, T. *Virology* 92(1): 31-45; 1979.

Nonproducer clones of Spafas chicken fibroblasts or erythroblasts transformed by strains R and ES4 of avian erythroblastosis virus (AEV) were isolated and characterized. They did not release virus particles detectable by ³H-uridine incorporation or reverse transcriptase assays. Transforming virus could be rescued from these clones by superinfection with avian leukosis viruses of subgroups A, B, C, and D. Analysis of ³⁵S-methionine-labeled cell extracts of the non-producer clones by immune precipitation showed that none of the three viral structural protein precursor polyproteins, Pr76gag, gPr95env, and Pr180gag-pol, were synthesized. Instead, a 75,000-dalton protein (AEV 75K) was isolated. By using specific antisera, this protein was shown to be antigenically related to the gag gene, but not to the pol or env genes. Pulse-chase experiments showed that the AEV 75K protein was turned over, but none of the major structural proteins (p27, p19, or p15) could be detected after the chase. Nonproducer cells expressed inhibitory activity only for p19 in competition radioimmunoassays; no inhibitory activity related to p27 or p15 could be demonstrated. Tryptic peptide analysis of the AEV 75K protein confirmed the immunological data in that the fingerprint of this protein was distinct from those of Pr76gag, gPr95env, and the β -subunit of reverse transcriptase. AEV 75K may play a role in transformation. (44 refs)

- 79-1538** **Ultrastructural Study of Avian Myelocytomatosis Virus (MC 29).** (Fre) Gogusev, J. (Laboratoire de Medecine experimentale, College de France, 11, place Marcelin-Berthelot, 75231 Paris Cedex 05, France); Heine, U. *C R Acad Sci [D] (Paris)* (287): 1075-1078; 1978.

The ultrastructure of the avian myelomatosis virus (MC 29) genome was studied in chick fibroblast cultures by electron microscopy, using a sucrose gradient to separate the high-mol-wt RNA's. Six dimers were found in the 100 molecules counted. The overall length of the molecules varied, which is indicative of degradation of the distal parts of the polynucleotide chain. The dimeric structures contained dimeric linkage structures but no hairpin loops. The length of the dimeric linkage structures averaged 3.8 μ m. After denaturation, the mean length of the 28S fraction was 1,248 μ m, which corresponds to a mol wt of 1.50×10^6 daltons. The 34S fraction had a length of 2,125 μ m and a mol wt of 2.55×10^6 daltons. (12 refs)

- 79-1539** **Use of a Block Copolymer as Primer for DNA Synthesis by Avian Myeloblastosis Virus (AMV) DNA Polymerase (Meeting Abstract).** (Eng) Weiss, G. B. (Univ. Texas Medical Branch, Galveston, TX, 77550); Carr, B. K. *Fed Proc* 38(3, part 1): 622; 1979. (no refs)

- 79-1540** **Avian Retrovirus Protein p19 May Regulate Processing of Viral mRNA (Meeting Abstract).** (Eng) Leis, J. P. (Duke Medical Center, Durham, NC, 27710); Scheible, P.; Smith, R. E. *Fed Proc* 38(3, part 1): 814; 1979. (1 ref)

- 79-1541** **Immunofluorescence on Avian Sarcoma Virus-transformed Cells: Localization of the src Gene Product.** (Eng) Rohrschneider, L. R. (Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104). *Cell* 16(1): 11-24; 1979.

The localization of the avian sarcoma virus src gene product (p60src) was examined by indirect immunofluorescence (IF) in chicken embryo fibroblasts (CEF) and normal rat kidney (NRK) cells transformed by the Schmidt-Ruppin strain of Rous sarcoma virus, subgroup D (SR-RSV-D). Antitumor serum precipitated p60src from SR-RSV-D-transformed CEF but not from CEF infected with a transformation-defective (td) mutant of SR-RSV-D. All viral structural proteins and precursors contained in these immunoprecipitates could be eliminated by competition with unlabeled virus. Similar results were obtained with NRK cells transformed by SR-RSV-D (SR-RK). With acetone-fixed cells, p60src-specific IF revealed a principal fluorescence pattern in both cell systems that was diffuse and situated in the cytoplasm. IF on formaldehyde-fixed cells also indicated the cytoplasmic location of p60src and revealed a specific subcytoplasmic concentration of the fluorescence. An additional fluorescence pattern was seen between cells in contact in both SR-RK and SR-RSV-D-transformed CEF. IF on viable cells suggested that p60src was not on the surface of these transformed cells. The fluorescence patterns were specific for avian sarcoma virus-transformed cells and were not found in uninfected cells, cells infected with a td mutant of SR-RSV-D, or cells transformed by an antigenically unrelated murine sarcoma virus. (46 refs)

- 79-1542** **Dissociation of Transformation Parameters Using Temperature-conditional Mutants of Rous Sarcoma Virus.** (Eng) Weber, M. J. (Dept. Microbiology, Univ. Illinois, Urbana, IL, 61801); Friis, R. R. *Cell* 16(1): 25-32; 1979.

Two alternative explanations were considered for the partial transformation properties of tsG1251, a mutant of Rous sarcoma virus that induces a partially transformed phenotype at 42 C: (1) the *src* gene product could have more than one intracellular target, and (2) tsG1251 could be a leaky mutant. Secondary cultures of chf chicken embryo body walls were infected with a variety of temperature-conditional transformation mutants at temperatures between the restrictive and permissive temperatures (36, 38, 40, or 42 C), and the following parameters of transformation were measured 2 days after the final plating: growth in soft agar, growth in the absence of serum, density-dependent growth inhibition, LETS (large, external, transformation-sensitive) protein on the surface, hexose transport rate, plasminogen activator activity, and adhesion to the culture dish. The properties of tsG1251 could not be mimicked by making any of the other mutants leak. Although all the transformation parameters varied coordinately with temperature in most of the mutant-infected cells, cells infected with tsG1251, while thermosensitive for cellular parameters of transformation, were cold-sensitive for growth. These results indicate that tsG1251 is not simply a leaky mutant and raises the possibility that *src* has more than one primary intracellular target. An alternative explanation for the dissociation of growth properties from cellular manifestations of transformation is that the tsG1251 *src* protein is altered either in its regulation or structure in such a way as to become growth inhibitory at low temperatures in cells infected with this mutant. (33 refs)

79-1543 Effects of Inhibitors of Lipid Synthesis on Transformation in Chick Embryo Fibroblasts Infected with Rous Sarcoma Virus. (Eng) Harley, J. B. (Dept. Internal Medicine, Yale Univ., New Haven, CT, 06510); Goldfine, H. *Exp Cell Res* 118(1): 47-54; 1979.

The effects of two inhibitors of lipid synthesis [25-hydroxycholesterol (HC) and cerulenin] on early events in the transformation of chicken embryo cells by a temperature-sensitive mutant of Rous sarcoma virus (RSV *tsLA24*) were studied. HC caused a dose-dependent inhibition of growth in uninfected cells and inhibited sterol synthesis in RSV *tsLA24*-infected cells. When infected cells were treated with HC starting 12 hr before shiftdown from the nonpermissive temperature (41 C) to the permissive temperature (35 C) or with cerulenin starting 2 hr before shiftdown, they were initially able to increase their uptake of 2-deoxyglucose. They were unable to maintain this enhanced rate, however, and the rate of 2-deoxyglucose uptake decreased to the level of the controls at the nonpermissive temperature. As indicated by ³H-thymidine uptake, the ability of RSV *tsLA24*-infected cells to enter the S phase when shifted to 35 C in serum-free medium was not inhibited by HC. It appears that in this system the early events of transformation can occur in a completely defined medium and that these early events do not require normal rates of sterol synthesis. (22 refs)

79-1544 The NH₂-Terminal Sequence of the Avian Oncovirus *gag* Precursor Polypeptide (Pr76gag).

(Eng) Palmiter, R. D. (Dept. Biochemistry, Univ. Washington, Seattle, WA, 98195); Gagnon, J.; Vogt, V. M.; Ripley, S.; Eisenman, R. N. *Virology* 91(2): 423-433; 1978.

To study the NH₂-terminal sequences of the avian oncovirus *gag* precursor polypeptide Pr76gag, 35S RNA from the Prague strain of Rous sarcoma virus (PR-RSV) was used to program the in vitro synthesis of Pr76gag under conditions that prevented acetylation of the NH₂-terminus. Using automated Edman degradation, the NH₂-terminal sequence of Pr76gag was identified as Ac-Met-Glu-Ala-Val-Ile-Lys-Val-Ile-X-X-Ala-X-Lys. This sequence represented the primary translation product and was not derived by processing of a precursor. Determination of the amino acid composition of the 19a and 19d peptides of the p19 virion protein indicated that 19a was probably the NH₂-terminal peptide of both Pr76gag and p19. The amino acid composition of the 19d peptide was not consistent with its lying at the NH₂ terminus of Pr76gag. Annealing the tRNA-Trp primer for reverse transcriptase to 35S viral RNA did not interfere with the synthesis of Pr76gag. Comparison of the amino acid sequence of Pr76gag with the previously reported nucleotide sequence of the 5' end of 35S RNA from PR-RSV showed that synthesis of Pr76gag is not initiated within the first 119 nucleotides of the viral genome. (36 refs)

79-1545 The Kinetics of Synthesis in Infectious Unintegrated Virus DNA in Rous Sarcoma Virus Infected Chicken Cells. (Eng) Stedman, N. (Dept. Cellular and Molecular Biology, Inst. Cancerology and Immunogenetics, Villejuif, France); Mariage, R.; Goubin, G.; Hillova, J.; Hill, M. *J Gen Virol* 42(1): 207-213; 1979.

The kinetics of the synthesis of supercoiled and nonsupercoiled virus DNA was studied in chicken embryo fibroblasts (CEF) infected with the Schmidt-Ruppin strain of Rous sarcoma virus (RSV) for different times. Secondary cultures of CEF were infected with RSV at a multiplicity of infection (moi) of 1-5 focus-forming units/cell and with a transformation defective (*td*) derivative at a moi of 1-5 infectious units/cell. Infectivity of the nucleic acids (DNA, RNA, and DNA-RNA hybrid) purified from the CEF after 3-24 hr of virus infection was determined by a transfection assay. Infectious virus nucleic acids were detected at 6 hr after infection for both RSV and the derivative. Twenty-four hours after infection, much larger amounts of infectious unintegrated DNA were recovered: 1,500 IU of *td* virus DNA and 7,800 IU of RSV DNA. The hybrid fraction was also infectious 24 hr after infection. Infectious supercoiled DNA could be recovered at 16 hr after infection. The specific infectivity of the supercoiled DNA was less than that of the nonsupercoiled fraction. Approx 8%, 6%, and 25% of the infectious DNA molecules had a supercoiled conformation at 1, 2, and 10 days after infection. Infectious unintegrated virus DNA was recovered 10 days after infection. The transfection assay confirmed that <1 cell in 10²-10³ chronically infected cells contains an unintegrated infectious DNA molecule. (29 refs)

- 79-1546 Characterization of Some Isolates of Newly Recovered Avian Sarcoma Virus.** (Eng) Halpern, C. C. (Rockefeller Univ., New York, NY, 10021); Hayward, W. S.; Hanafusa, H. *J Virol* 29(1): 91-101; 1979.

The biological and biochemical characteristics of newly recovered avian sarcoma virus (rASV) isolated from tumors of chickens injected with transformation-defective (*td*) mutants of the Schmidt-Ruppin strain of Rous sarcoma virus (SR-RSV) were studied. High titers of rASV's were generally obtained by cocultivation of tumor cells with normal chicken embryo fibroblasts or by homogenization of tumor tissues. All rASV isolates tested belonged to the same subgroup (A) as that of the *td* viruses from which they were derived, and the *gag* gene of the rASV's appeared to be derived from the *td* virus. Most rASV's were nondefective, although several isolates recovered from chickens infected with one *td* mutant appeared to be defective in replication. Sucrose sedimentation data indicated that the rASV's from several *td* isolates contained genomic RNA that was the same size as that from SR-RSV-A but 300-500 nucleotides larger than that of the parental *td* RNA. An *src*-specific complementary DNA probe hybridized 7%-30% to RNA's from various *td* viruses and approx 95% to RNA's from two isolates of rASV. Thus, the generation of rASV from *td* viruses involves the acquisition of new *src*-specific information. The data strongly suggest that the generation of rASV involves a genetic interaction between *td* virus and host cell genetic information. (36 refs)

- 79-1547 Oligosaccharide Chains of Avian RNA Tumor Virus Glycoproteins Contain Heterogeneous Oligomannosyl Cores.** (Eng) Hunt, L. A. (Dept. Microbiology, Univ. Kansas Medical Center, Coll. Health Sciences and Hosp., Kansas City, KS, 66103); Wright, S. E.; Etchison, J. R.; Summers, D. F. *J Virol* 29(1): 336-343; 1979.

To study the oligosaccharide chains of avian tumor virus, pronase-digested glycopeptides from purified Prague strain Rous sarcoma virus subgroups B and C (PrB-RSV and PrC-RSV, respectively) were analyzed by gel filtration coupled with specific exoglycosidase (EG) and endo- β -N-acetylglucosaminidase D (EAGA) digestions. A large fraction of the glycopeptides from purified PrB-RSV was sensitive to the combined EG and EAGA digestion. The oligosaccharide chains on these glycosidase-sensitive glycopeptides were heterogeneous with respect to the size of their oligomannosyl cores, containing similar amounts of 3-mannose and 5-mannose structures. With the (2-³H)-mannose-labeled glycopeptides from PrC-RSV, most of the oligosaccharide chains were high-mol-wt acidic structures with similar numbers of 3-mannose and 5-mannose core structures. (32 refs)

- 79-1548 Is the Product of the *src* Gene a Promoter?** (Eng) Bissell, M. J. (Lab. Chemical Biodynamics, Lawrence Berkeley Lab., Univ. California, Berkeley, CA,

94720); Hatie, C.; Calvin, M. *Proc Natl Acad Sci USA* 76(1): 348-352; 1979.

The effect of treatment with the tumor promoter 12-O-tetradecanoylphorbol 13-acetate (TPA) was studied in normal primary avian tendon (PAT) cells and chicken embryo fibroblasts (CEF) and in PAT and CEF cells infected with a temperature-sensitive (*ts*) mutant of Rous sarcoma virus (RSV; LA24). 2-Deoxy-D-glucose (2-dGlc) uptake, collagen synthesis, and morphology were assessed as indicators of transformation. Addition of TPA to normal cells maintained at 41 C resulted in increased 2-dGlc uptake and a decreased collagen synthesis but the changes were smaller than those occurring after transformation. Addition of TPA to LA24-infected cells at 41 C (the nonpermissive temperature) produced changes that were close to or even more drastic than those in LA24-infected cells grown at 35 C. Morphologically, LA24-infected PAT cells at 41 C appeared entirely transformed by 10 hr. In a shift-down experiment, cells shifted in the presence of TPA for 12 hr were morphologically similar to cells that had been shifted to 35 C for 24-36 hr in the absence of TPA. Attempts to produce foci with LA24-infected cells at 41 C in the presence of TPA were unsuccessful. However, significant morphological alterations of LA24-infected CEF were produced in semisoft agar after 24 hr of treatment at 41 C. Under the same conditions, normal cells showed only an increase in criss-cross patterns. It is proposed that viral carcinogenesis occurs in two stages: an initiation step caused by the expression of a part of viral genome other than *src* and a promotion step caused by the activation of the *src* gene. The *src* gene product could be enhanced or replaced by other promoting agents. (39 refs)

- 79-1549 Effects of the *src* Gene Product on Microfilament and Microtubule Organization in Avian and Mammalian Cells Infected with the Same Temperature-Sensitive Mutant of Rous Sarcoma Virus.** (Eng) Wang, E. (Rockefeller Univ., New York, NY, 10021); Goldberg, A. R. *Virology* 92(1): 201-210; 1979.

The cytoskeletal organization was studied in rat kidney cells (RKC) and chick embryo fibroblasts (CEF) transformed by a temperature-sensitive (*ts*) *src* mutant (LA25) of Rous sarcoma virus (RSV). At the nonpermissive temperature (39.5 C), LA25-infected RKC displayed a well-defined network of actin-containing fibers that represented bundles of microfilaments of 50-70 A. Within 12-24 hr of shifting to the permissive temperature (33 C), > 95% of the actin fibers had disappeared from the cytoplasm. Their organization became unrecognizable and the cell shape was of the transformed phenotype. Microtubule organization, however, remained intact upon shifting from the nonpermissive to the permissive temperature. RKC transformed by RSV grew in soft agar and formed colonies at the permissive temperature. In LA25-infected CEF, both microfilament and microtubule organization was lost shortly after the shift to the permissive temperature. These results show that the LA25 *src* gene product can differentially affect the organization of microtubules

and microfilaments. It is possible that avian cells allow the synthesis of *src* gene product in sufficient amounts to cause considerable alterations in microtubular organization, whereas the level of *src* in rat kidney cells may not be sufficient to alter microtubule distribution. The results also suggest that the absence of microfilament bundle organization, but not necessarily microtubule organization, may be a factor in determining if a cell can grow in an unregulated fashion in an animal. (18 refs)

79-1550 Effect of Immunological Intervention on In Vivo Murine Rous Sarcoma Virus Tumorigenesis (Meeting Abstract). (Eng) Babcock, G. F. (Univ. North Carolina Medical Sch., Chapel Hill, NC, 27514); Banks, R.; Whitmore, A. C.; Haughton, G.; Schwab, J. H. *Fed Proc* 38(3, part 2): 1176; 1979. (no refs)

79-1551 Expression of RSV Induced Tumor Membrane Antigen and Phenotypic Transformation (Meeting Abstract). (Eng) Comoglio, P. M. (Dept. Histology, Univ. Trieste Sch. Medicine, Trieste, Italy); Prat, M.; Tarone, G. *Fed Proc* 38(3, part 2): 1106; 1979. (1 ref)

79-1552 Biochemical Structure and Antigenic Composition of Plasma Membrane of Rous Sarcoma Virus Transformed Fibroblasts (Meeting Abstract). (Eng) Comoglio, P. (Istituto di Istologia e Embriologia, Facoltà di Medicina, Università di Trieste, Trieste, Italy); Bertini, M.; Prat, M.; Tarone, G. *Ital J Biochem* 27(4): 268-270; 1978. (8 refs)

79-1553 On the Reduced Intercellular Adhesiveness of Virally Transformed BHK21 Cells. (Eng) Edwards, J. G. (Dept. Cell Biology, Univ. Glasgow, Glasgow G12 8QQ, Scotland); Dysart, J. M.; Edgar, D. H.; Robson, R. T. *J Cell Sci* 35: 307-320; 1979.

The intercellular adhesiveness of normal and virally transformed baby hamster kidney (BHK21) cells was compared under a variety of conditions. The cells were transformed by either polyoma or Rous sarcoma virus (RSV). In a long-term aggregation assay, cells were resuspended in complete growth medium and incubated in a gyratory shaker for 18-24 hr. The untransformed BHK21 clone 13 (C13) cells yielded firm spherical aggregates. The transformed cells aggregated much less than the C13 cells, and the aggregates that were formed appeared to be unstable. This difference could be measured by electronic particle counting or by filtering aggregated suspensions of ³²P-labeled cells through fabric filters of various pore sizes. The aggregation difference was not dependent on exposure to trypsin. The presence of ϵ -aminocaproic acid (10 mg/ml), an inhibitor of plasmin activation, during aggregation did not enhance the aggregation of transformed derivatives. BHK cells transformed by the Bryan strain of RSV aggregated in a short-term (45 min) assay but not in the

long-term assay. When suspended cells were seeded onto confluent sheets of cells of like type, none of the transformed lines showed a marked reduction, compared with C13 cells, in ability to adhere. The decreased aggregation of transformed cells in the long-term assay is consistent with suggestions that the large, external, transformation-sensitive (LETS) protein is involved in the intercellular adhesion of fibroblasts. It is suggested that the short-term aggregation of freshly trypsinized cells may depend on the secretion of LETS from an intracellular pool. (45 refs)

79-1554 Diamine Oxidase and Polyamine Oxidase Activities in Normal and Transformed Cells. (Eng) Quash, G. (Unité de Virologie Fondamentale et Appliquée, I.N.S.E.R.M.-U.51, Lyon Cedex 2, France); Keolouangkhot, T.; Gazzolo, L.; Ripoll, H.; Saez, S. *Biochem J* 177(1): 275-282; 1979.

The diamine oxidase activity of normal rat kidney cells and cells transformed by avian sarcoma virus was compared to determine whether there is a direct relationship between this activity and cell growth. For both cell types, diamine oxidase activity rose during the lag phase after seeding, was highest at 24 hr, and decreased during the exponential phase of growth. The activity in transformed cells was 50% greater than that in normal cells at 24 hr, was twofold lower at saturation density, and was three- to fourfold lower at confluence. The presence of free intracellular putrescine was not responsible for the difference. Differences of about the same order of magnitude were observed between transformed and normal human, chicken, and rat cells. Polyamine activity also varied with the growth of transformed rat kidney cells, but it showed no significant variation from normal between 24 and 96 hr after seeding. The activity in cells at confluence was three- to fivefold lower in the transformed cells than in the normal cells. A similar 5- to 10-fold decrease in activity was seen in 9,10-dimethylbenz(a)anthracene-induced rat mammary tumors and in human esophageal tumors. (27 refs)

79-1555 Decreased Production of Transforming Virus and Altered Antigenic Behaviour in Cultured Avian Sarcoma Cells. (Eng) Wainberg, M. A. (Lady Davis Inst. Medical Res., Jewish General Hosp., Montreal, Canada); Yu, M.; Israel, E. *J Gen Virol* 42(2): 255-264; 1979.

Transforming virus production and antigenic behavior were examined in cultured avian sarcoma cells derived from young birds carrying progressively growing sarcomas or from older animals carrying regressing neoplasms. Cultivated tumor cells from mature chickens that had been injected with avian sarcoma viruses (ASV) were defective in producing either transforming or oncogenic virus, but they sometimes synthesized incomplete physical particles, as measured by RNA-dependent DNA polymerase (RDDP) activity. Tumor cells derived from progressively growing neoplasms synthesized large quantities of fully transforming oncogenic progeny virus and RDDP. After varying periods of culture (25-30

days and 4-5 passages), production of both transforming virus and RDDP fell off dramatically. However, the long-term-cultured tumor cells remained fully oncogenic following injection into susceptible chickens, indicating that the genetic information needed to induce tumor growth continued in the absence of virus production. Supernatant fluids from freshly cultivated (3-4 days) tumor cells derived from regressing malignancies were unable to stimulate the lymphocytes of tumor-bearing chickens. Supernatant fluids from ASV-transformed chicken embryo fibroblasts or from cultures of tumor cells from progressing neoplasms were equally efficient as specific antigens. Following multiple passages and extended growth in culture, however, the ability of these tumor cell fluids to stimulate the lymphocytes of sensitized hosts diminished concomitantly with the capacity of these cells to synthesize progeny virus. Thus, tumor cells that are derived from progressively growing malignancies and that senesce in culture closely resemble tumor cells that have aged in vivo. (24 refs)

- 79-1556 Translation of Avian Sarcoma Virus RNA in *Xenopus laevis* Oocytes.** (Eng) Katz, R. A. (Dept. Microbiology, Coll. Physicians and Surgeons, Columbia Univ., New York, NY, 10032); Maniatis, G. M.; Guntaka, R. V. *Biochem Biophys Res Commun* 86(2): 447-453; 1979.

Studies demonstrating the synthesis and posttranslational processing of Pr76 (a 76,000-dalton precursor protein to group-specific antigens p27, p19, and p12/15) after microinjection of avian sarcoma virus 35S subunits or aggregated 60S-70S virion RNA are presented. Bound transfer RNA-trp primer did not appear to affect the capacity of 35S virion RNA to direct protein synthesis. (20 refs)

- 79-1557 Further Study on the Three-Dimensional Structure of the Core of Marek's Disease Virus and Herpesvirus of Turkey.** (Eng) Okada, K. (Dept. Comparative Pathology, Faculty Veterinary Medicine, Hokkaido Univ., Sapporo, Japan); Fujimoto, Y.; Nakanishi, Y. H.; Onuma, M.; Mikami, T. *Arch Virol* 59(1/2): 137-144; 1979.

The three-dimensional structures of the cores of Marek's disease virus (MDV) and herpesvirus of turkeys (HVT) were examined with the use of a tilting apparatus attached to an electron microscope. Quail fibroblast cultures were infected with the JM strain of MDV and the FC 126 strain of HVT; the Cal-1 strain of MDV in a chick kidney cell culture was also used. Immature virus particles were found in the nuclei of the MDV- and HVT-infected cells. Numerous small nuclear particles and cross-shaped capsids were found in HVT-infected cells, and empty capsids, which appeared to lack cores, were seen in cells infected with either virus. Some capsids had cores consisting of crossed toroids surrounding a cylindrical mass. The toroids were 10-20 nanometers (nm) thick with an outside diameter of 68 nm. A semicircular toroid and a core with two toroids were also detected. En-

veloped particles of different sizes were found in the nuclear vesicles and endoplasmic reticulum. The cores of these particles and those of the naked capsids consisted of numerous electron-opaque bands 10-20 nm thick. It is possible that the pleomorphic structures of the core may represent developmental stages of the viruses. (11 refs)

- 79-1558 The Genetics of Resistance to Mammary Tumor Virus Infection and Tumorigenesis in C57BL/CRGL Mice (Meeting Abstract).** (Eng) Danilovs, J. A. (Univ. California, Berkeley, CA). *Diss Abstr Int B* 39(8): 3682; 1979. (no refs)

- 79-1559 Mouse Mammary Tumor Virus Genes: Regulation of Expression by Glucocorticoids and Structural Analysis with Restriction Endonucleases.** (Eng) Ringold, G. M. (Dept. Biochemistry, Univ. California, San Francisco, CA, 94143); Cohen, J. C.; Ring, J.; Shank, P. R.; Varmus, H. E.; Yamamoto, K. R. *J Toxicol Environ Health* 4(2/3): 457-470; 1978.

The effects of treatment with glucocorticoid hormones (eg, dexamethasone: DEX) on the production of mouse mammary tumor virus (MMTV) in a mouse mammary tumor cell line (GR) and a rat hepatoma line (HTC) were studied. These cell lines contain specific glucocorticoid receptors detectable by the binding of ³H-DEX in whole cells or in cell extracts. DEX stimulated MMTV production. The reaction appeared to be a primary effect of the receptor-steroid complex, as a result of which the rate of synthesis of MMTV RNA was selectively increased. Viral RNA synthesis was stimulated 10-20 times in GR cells and at least 20 times in HTC cells. The rate of viral RNA synthesis reached a max within 15 min after addition of the hormone. The amount of MMTV DNA and the level of expression of these viral genes were determined in independently isolated clones of infected HTC cells by measuring the kinetics of annealing of ³H-MMTV complementary DNA to cell DNA or cell RNA. Although clones containing many copies of viral genes tended to produce more viral RNA in the presence of DEX than clones containing few MMTV DNA copies, this correlation was not a strict one. Of the clones examined, all that produced basal levels of MMTV RNA were stimulated to produce increased quantities by DEX; however, the extent of MMTV RNA induction by DEX varied greatly from clone to clone (50- to 1,000-fold) in a manner that had no apparent relation to the number of integrated viral genes. It is conceivable that not all of the integrated viral genomes are being transcribed to an equal extent in the absence of DEX and that not all of them are stimulated to an equal extent in its presence. Unintegrated MMTV DNA remaining in chronically infected HTC cells was used as substrate to investigate the chromosomal loci at which viral genes integrate. Treatment with nine restriction endonucleases indicated that there are many sites in cellular DNA into which MMTV DNA can integrate, and that these sites may be a determining factor for MMTV RNA synthesis. (37 refs)

- 79-1560 Endogenous Mouse Mammary Tumor Virus DNA Is Distributed Among Multiple Mouse Chromosomes.** (Eng) Morris, V. L. (Dept. Microbiology and Immunology, Univ. Western Ontario, London, Ontario N6A 5C1, Canada); Kozak, C.; Cohen, J. C.; Shank, P. R.; Jolicoeur, P.; Ruddle, F.; Varmus, H. E. *Virology* 92(1): 45-55; 1979.

The distribution of endogenous mouse mammary tumor virus (MMTV)-specific DNA in the genome of A/HeJ mice was examined with the use of molecular hybridization and restriction endonucleases to analyze DNA from mouse-hamster hybrid clones that segregate mouse chromosomes. MMTV DNA sequences were present on at least three separate pairs of mouse chromosomes. Chromosome pair 4 contained two copies of MMTV DNA. Four copies of MMTV proviral sequences were located within chromosome pair 15 and 17. An additional unit of viral DNA segregated independently, although its location is ambiguous. The results obtained by kinetic analysis of DNA extracted from the mouse-hamster clones are in reasonable agreement with the data obtained by restriction endonuclease analysis. These findings coupled with those from other reports imply that the endogenous proviruses were acquired by independent infections of the germ line of individual progenitor mice and have since segregated during the development of inbred strains. (35 refs)

- 79-1561 Simultaneous Production of Casein and Mammary Tumor Virus in Mouse Mammary Epithelial Cells Grown on Floating Collagen Gels.** (Eng) Enami, J. (Dept. Physiology, Dokkyo Univ. Sch. Medicine, Mibu, Tochigi 321 02, Japan); Yang, J.; Nandi, S. *Cancer Lett* 6(2): 99-105; 1979.

The simultaneous production of casein and mammary tumor virus (MTV) in response to hormones was analyzed in monolayer cultures of mammary epithelial cells from MTV-infected pregnant BALB/cfC3H mice. A comparison of the two cell culture substrata, plastic culture dishes and floating collagen gels, showed that the latter supported a much higher degree of simultaneous casein and MTV production in response to hormones. Among the three different combinations of hormones used, insulin alone, insulin + cortisol, or insulin + cortisol + prolactin, the latter stimulated max casein and MTV production in serum-free culture medium. The importance of the floating collagen gels was further shown by delaying the flotation of the gels. When the release of the gels was delayed, there were concomitant delays in the increase of casein and MTV production. These results indicate that hormones, the nature of the substratum, and flotation regulate the degree of differentiation of mammary epithelial cells in vitro. (18 refs)

- 79-1562 Phosphoproteins of the Murine Mammary Tumor Virus.** (Eng) Sarkar, N. H. (Memorial

Sloan-Kettering Cancer Center, New York, NY, 10021); Whittington, E. S.; Racevskis, J.; Marcus, S. L. *Virology* 91(2): 407-422; 1978.

To determine whether any of the structural components of murine mammary tumor virus (MuMTV) are phosphorylated, MuMTV labeled in vivo with [³²P]orthophosphate and ³H-amino acids was analyzed on cylindrical sodium dodecyl sulfate (SDS)-polyacrylamide gels. Of the five major polypeptides of MuMTV (gp47, gp34, p27, p16 and p12), ³²P comigrated to a great extent with p23 and to a lesser extent with p27. Further analysis by hydrophobic chromatography, gel electrophoresis, slab gel electrophoresis, and Bio-Gel A 5m chromatography identified p23 and p27 as phosphoproteins. Radioimmunoprecipitation indicated that p23 is not antigenically related to p27 and suggested that p23, although a minor protein component of MuMTV, is an independent entity and the major phosphoprotein of this virus. Both p27 and p23 contained phosphoserine, and some p27 preparations appeared to contain phosphothreonine. (33 refs)

- 79-1563 Structural Components of Mouse Mammary Tumor Virus. III. Composition and Tryptic Peptides of Virion Polypeptides.** (Eng) Yagi, M. J. (Dept. Neoplastic Diseases, Mount Sinai Sch. Medicine, 5th Ave. at 100th St., New York, NY, 10029); Tomana, M.; Stutzman, R. E.; Robertson, B. H.; Compans, R. W. *Virology* 91(2): 291-304; 1978.

The compositions and possible structural interrelationships among mouse mammary tumor virus (MMTV) proteins were examined following their isolation by preparative sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Their tryptic peptides and glycopeptides were analyzed, and their amino acid and carbohydrate compositions were determined. The minimal carbohydrate content was 9.3% for gp52, 11.2% for gp37.7, and 19.4% for gp33. The carbohydrate moieties of all three glycoproteins were similar in composition, and they contained fucose, mannose, galactose, N-acetylglucosamine, and N-acetylneuraminic acid. One major size class of oligosaccharide side chain was generated from each glycoprotein by pronase digestion of gp52, gp37.7, and gp33. The mol wts of these glycoprotein size classes were 3,200-3,600 for gp52, 3,750-4,250 for gp37.7, and 3,200-3,700 for gp33. Tryptic peptide patterns of MMTV glycoproteins demonstrated that many of the peptides from gp37.7 and gp33 were similar in size and charge. However, comparison of the tryptic peptides of gp52 with those from gp37.7 and gp33 indicated that gp52 was not structurally related to the other two glycoproteins. SDS-PAGE profiles obtained after limited trypsin digestion of gp52, gp37.7, and gp33 resolved two carbohydrate-containing peptides from each glycoprotein, that appeared to be of similar size. Analyses of tryptic peptides of the five nonglycosylated MMTV proteins p46, p24, p17, p13, and p8 indicated that these proteins possess distinct amino acid sequences. (46 refs)

79-1564 Development of an Isotopic Staphylococcal Protein A Test for Detection of Cell Surface Mammary Tumor Virus Antigens (Meeting Abstract). (Eng) Callis, A. H. (Univ. Tennessee, Memphis, TN, 38163); Ritzl, E. M. *Fed Proc* 38(3, part 2): 911; 1979. (no refs)

79-1565 Localization of Murine Mammary Tumor Virus Polypeptides on the Surface of Tumor Cells. (Eng) Westenbrink, F. (Radiobiological Inst., TNO, Rijswijk, Netherlands); Koornstra, W.; Creemers, P.; Brinkhof, J.; Bentvelzen, P. *Eur J Cancer* 15(1): 109-121; 1979.

Antisera raised in rabbits against three of the major viral polypeptides of murine mammary tumor viral (MMTV), a glycoprotein with a mol wt of 52,000 daltons (gp52) and two polypeptides with a mol wt of 28,000 and 12,000 daltons (p28 and p12, respectively), were used to assay these viral constituents on the cell membrane. No significant cross-reactivity was detected among the three antisera by immunodiffusion, immunoelectrophoresis, and radioimmunoassay, indicating that the three MMTV components are immunologically unrelated. In a fixed-cell immunofluorescence assay using the three antisera, gp52, p28, and p12 were detected in the cytoplasm of murine mammary tumor cell lines Mm5mt/c1 and C3HMT/C111, as well as in the murine leukemia cell lines GRSL18 and L1210. No virus-specific fluorescence was observed in the mammary tumor line EMT-6, which does not release MMTV. The concentration of gp52 in the cytoplasm was considerably lower than that of p28 and p12. In the membrane immunofluorescence assay, only gp52 proved to be localized on the cell surface. In humoral cytotoxicity tests, only antiserum to gp52 gave positive reactions with Mm5mt/c1, L1210, and GRSL18. The serum did not react with BALB/3T3 cells infected with Rauscher murine leukemia virus. The prevalence of gp52 on the cell surface suggests that this antigen is the best candidate for future vaccination studies. (30 refs)

79-1566 Intracytoplasmic Type A Particles from Mammary Tumours and Leukaemias of Strain ICRC Mice. (Eng) Karande, K. A. (Biology Div., Cancer Res. Inst., Tata Memorial Centre, Parel, Bombay 400 012, India); Joshi, B. J.; Talageri, V. R.; Dumaswala, R. U.; Ranadive, K. J. *Br J Cancer* 39(2): 132-142; 1979.

The morphological, biophysical, immunological, and structural characteristics of intracytoplasmic A-type particles from ovarian hormone-induced leukemias of strain ICRC mice and mammary tumors of ICRC and C3H(Jax) mice were studied. The purified virions banded at a density of 1.20 g/ml in 12%-60% sucrose gradients after spinning at 113,000 g for 4 hr. Gel electrophoresis indicated that the A particles from mammary tumors contained seven to eight polypeptides ranging in size from 14,000 to 100,000 daltons, and that their leukemia A particles contained eight polypeptides ranging from 10,000 to 74,000 daltons. All bands were PAS-negative. Immunodiffusion and immunoelectrophoresis indicated that

the leukemia and mammary tumor A particles had common antigens and that three proteins of mouse mammary tumor virus were antigenically similar to those of A particles. Purified A virus preparations were inoculated into ICRC and DBA-MTI sucklings. One of 8 inoculated ICRC females and 2/10 control ICRC females developed breast adenocarcinomas, and 2 inoculated ICRC males developed leukemias. Of 6 inoculated DBA-MTI females, 1 developed leukemia, 1 developed a spleen tumor, and 1 developed a cervical tumor; DMBA-MTI males remained tumor-free. The ICRC mouse is a good model for studying hormone:viral interactions in carcinogenesis. (37 refs)

79-1567 Mechanisms of Leukemogenesis. I. Generation of Autoreactive Lymphocytes in Response to a Murine Leukemia Virus (Meeting Abstract). (Eng) Schenk, P. J. (Downstate Medical Center, Brooklyn, NY, 11203); Howe, M. L. *Fed Proc* 38(3, part 2): 1072; 1979. (no refs)

79-1568 Phenotypic Mixing Between Murine Leukemia Viruses: Characteristics of Ecotropic Virus Infection of Heterologous Cells. (Eng) Ishimoto, A. (Lab. Viral Diseases, NIH, Bethesda, MD, 20014); Hartley, J. W.; Rowe, W. P. *Virology* 91(2): 464-471; 1978.

Aspects of ecotropic murine leukemia virus (MuLV) infection of heterologous cells achieved by phenotypic mixing were studied. The nomenclature used for the different classes of virions is the genotype followed by the host range phenotype in parentheses; X = xenotropic, M = ecotropic. Both xenotropic [X(x)] and phenotypically mixed [M(x)] particles infected mink, rabbit, duck, guinea pig, human, and cat cells, but not chicken C/O cells. There was generally correspondence between the titers of M(x) and X(x) virions detected. Mink cell cultures inoculated with the M(x) pools showed XC plaques when subjected to the direct UV-XC plaque development assay. These plaques arose by proliferation of the cells infected in the first cycle of infection, and there was no evidence for XC-positive, mink-infectious competent virions in the preparation. Clonal lines of mink and rabbit cells chronically infected with N-tropic ecotropic (AKR-L1), B-tropic ecotropic (WN1802B), and NB-tropic ecotropic (Friend) MuLV were established. Virtually all cells produced virus but at a generally low rate. The infectivity titers were 1 to 3 log₁₀ lower than those obtained with ecotropic viruses in mouse cells or with xenotropic viruses in mink cells or in the rabbit corneal cell line SIRC. Also, the number of cells that registered positive by immunofluorescent staining with MuLV antiserum was generally low. These viruses showed ecotropism and the same *Fv-1* restriction patterns as the input viruses through more than 6-12 mo of chronic virus production in the heterologous cells. Treatment with 5-iododeoxyuridine enhanced virus production up to 10-fold in 3/4 lines tested and increased fluorescent antibody staining two- to fourfold in two lines. Dexamethasone treatment slightly increased virus production in two lines. The infected lines were

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sensitive to superinfection with xenotropic MuLV and with feline leukemia virus. (20 refs)

- 79-1569 XenCSA: Cell Surface Antigens Related to the Major Glycoproteins (gp70) of Xenotropic Murine Leukemia Viruses.** (Eng) Morse, H. C. (Lab. Microbial Immunity, Natl. Inst. Allergy and Infectious Diseases, NCI, NIH, Bethesda, MD, 20014); Chused, T. M.; Boehm-Truitt, M.; Mathieson, B. J.; Sharrow, S. O.; Hartley, J. W. *J Immunol* 122(2): 443-454; 1979.

Antisera from rabbits immunized with xenotropic murine leukemia virus (MuLV)-infected rabbit corneal (SIRC) cells were tested for patterns of reactivity with thymocytes and spleen cells of inbred mouse strains. The antisera contained antibodies with class-specific reactivity for a set of gp70 molecules coded for by xenotropic MuLV. The antigens recognized by these sera were designated XenCSA for xenotropic MuLV envelope-related cell-surface antigens. Using flow microfluorometry, thymocytes and spleen cells from 63 strains of inbred mice showed a wide range of XenCSA expression that could be divided into three basic phenotypic patterns: high XenCSA expression on both thymocytes and spleen cells (19 strains); low expression on thymocytes but high expression on spleen cells (17 strains); and low expression on both cell populations (27 strains). Expression of XenCSA was highly correlated with expression of G-IX on thymocytes, but it was not correlated with expression of Fv-1, T1a, H-2, Pca-1, or Gross cell-surface antigen. The level of XenCSA expression was also independent of the amount of infectious xenotropic MuLV produced by the cell. An antigen related to XenCSA was found to circulate in the serum of some but not all strains of mice expressing the cell-surface antigen. The data indicate that antigens related to the gp70 of xenotropic MuLV are a normal surface constituent of lymphocytes from all inbred mouse strains. (63 refs)

- 79-1570 RNA Sequencing Provides Evidence for Allelism of Determinants of the N-, B- or NB-Tropism of Murine Leukemia Viruses.** (Eng) Rommelaere, J. (Dept. Biology, Center Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139); Donis-Keller, H.; Hopkins, N. *Cell* 16(1): 43-50; 1979.

Three large RNase T1-resistant oligonucleotides (ON's) previously shown to be genetically associated with either the N-, B-, or NB-tropism of C-type murine leukemia viruses of BALB/c origin were sequenced. The three ON's, which lie in the 5' third of the ON maps of their respective viruses, were found to share a 10-base sequence. These observations suggest that the determinants of N-, B-, or NB-tropism monitored by the three ON's are allelic. The ON's associated with N- and B-tropism differed in sequence at 4/16 nucleotides, but the B- and NB-tropism-associated ON's differed in sequence by only 1/16 bases. These results are consistent with the possibility that B-tropic viruses arise from N-tropic viruses by recombination, but NB-tropic viruses arise from

B-tropic viruses by mutation. Two T1 ON's, designated 12 and 35, that comigrate with the N and B ON's, respectively, in two-dimensional gel electrophoretic fingerprints of N- and B-tropic viruses, were also sequenced. ON's 12 and 35 are present in the N-, B- and NB-tropic viruses of BALB/c origin that were analyzed. ON's N and 12 shared 10 bases of their sequence, although these were not the same 10 bases shared by the three tropism ON's. The possible significance of this sequence repetition in the N and 12 ON's, which lie in opposite thirds of the genome, is not known. (24 refs)

- 79-1571 Chronic Blastogenesis of Endogenous Viral Antigen(s): A Possible Mechanism for C-Type Viral Leukemogenesis (Meeting Abstract).** (Eng) Lee, J. C. (Cancer Biology Program, NCI, Frederick Cancer Res. Center, Frederick, MD, 21501); Ihle, J. N. *Fed Proc* 38(3, part 2): 1451; 1979. (1 ref)

- 79-1572 Cytotoxic Murine T Cells Directed Against AKR/Gross Virus-induced Tumors (Meeting Abstract).** (Eng) Green, W. R. (Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104); Nowinski, R. C.; Henney, C. S. *Fed Proc* 38(3, part 2): 1466; 1979. (no refs)

- 79-1573 The Nature of the Association Between the Murine Leukemia Virus Envelope Proteins.** (Eng) Pinter, A. (Sloan-Kettering Inst. Cancer Res., 1275 York Ave., New York, NY, 10021); Lieman-Hurwitz, J.; Fleissner, E. *Virology* 91(2): 345-351; 1978.

The amount of gp70 and p15(E), the two major murine leukemia virus (MuLV) envelope proteins, present as a disulfide-linked complex ([gp90]) was assayed for several MuLV preparations. Upon dissociation of AKR MuLV with 1% sodium dodecyl sulfate (SDS) under nonreducing conditions, approx 10% of the gp70 molecules were found in the form of [gp90]; disruption with 0.5% Nonidet P-40 (NP-40) prior to addition of SDS increased this percentage to 39%. For Rauscher MuLV, [gp90] was not observed after disruption directly with SDS; upon incubation with NP-40 prior to SDS treatment, increasing amounts of the complex were formed. Pretreatment with iodoacetamide did not inhibit the subsequent formation of [gp90] in the presence of NP-40. Exposure of virions to the thiol-specific reagents 2,2'-dithiobis(m-nitropropyridine) or N-ethylmaleimide resulted in quantitative conversion of gp70 to [gp90]. When these latter reactions were used to test for the noncovalent association of gp70 and p15(E), it was demonstrated that the two proteins maintained their native association in the presence of 0.5% NP-40, both in high- and low-salt concentrations. These results indicate that (1) a stable, intermolecular disulfide-linked gp70-p15(E) complex can form spontaneously after disruption of virions with nonionic detergents, and after activation of sulfhydryl groups of the membrane proteins and (2) the complex is not present in large quantities in the intact virions. (19 refs)

- 79-1574 Selective Packaging of Host tRNA's by Murine Leukemia Virus Particles Does Not Require Genomic RNA.** (Eng) Levin, J. G. (Lab. Molecular Genetics, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20014); Seidman, J. G. *J Virol* 29(1): 328-335; 1979.

The role of genomic RNA in transfer RNA (tRNA) selection was studied by comparing the composition of free 4S RNA in normal murine leukemia virus (MuLV: strains AKR-L1 and Moloney) and actinomycin D (A-D: 0.1 µg/ml)-treated virions, which lack genomic RNA (A-D virions). Although the A-D and normal virions contained approx the same amounts of RNA per virion, the 70S/4S ratio of the normal virions was eightfold greater than that of the less infective A-D virions. Virtually all of the 4S RNA in cell preparations of normal and A-D virions was contained within the virus particles. Normal and A-D virions contained the same population of tRNA's and in similar proportions, which suggests that the tRNA composition of MuLV particles is not determined by the viral RNA genome. Oligonucleotide fingerprinting of normal and A-D virion RNA revealed an identical spot that closely corresponded to the published fingerprint for Moloney MuLV tRNA-Pro. A possible role for one or more viral proteins, including reverse transcriptase, is suggested. (58 refs)

- 79-1575 Interactions of Murine Leukemia Virus (MuLV) with Isolated Lymphocytes. IV. The Role of Mitogen-induced Cellular DNA Synthesis in Virus Infection and Replication.** (Eng) Cerny, J. (Dept. Microbiology, Harvard Univ. Sch. Public Health, Boston, MA, 02115); Isaak, D. D. *Int J Cancer* 23(2): 260-268; 1979.

The requirement for lymphocyte (LC) activation with mitogen during in vitro infection with murine leukemia virus (MuLV) of Friend virus complex (FV) and the suppressive effects of MuLV on mitogen-induced LC activation were studied in short-term suspension cultures. LC's were infected with FV and then resuspended in medium with or without mitogens. Cells releasing infectious MuLV were enumerated as infectious centers (IC) on sarcoma virus +, leukemia virus-fibroblasts. The accumulation of IC followed a biphasic curve characterized by a plateau between days 1 and 4 and by a 10-fold increase in IC between days 5 and 7. Stimulation with a B-cell mitogen, bacterial lipopolysaccharide (LPS), following infection increased the number of IC 10- to 40-fold. Stimulation with a T-cell mitogen, concanavalin A (Con A), did not appreciably increase the number of IC on day 5 postinfection. In addition, there was a comparable enhancement of IC in cultures stimulated with LPS 2 days prior to or immediately after FV infection and in those not stimulated until 2 days after infection. Treatment of FV-infected, LPS-stimulated LC's with 5,6-bromodeoxyuridine (BUdR) and visible light at 2 days abolished cellular DNA and RNA synthesis but did not diminish subsequent MuLV replication; however, cellular DNA and RNA synthesis as well as MuLV replication were inhibited in LPS-stimulated cells treated

with BUdR and light prior to FV infection. The uptake of ³H-thymidine and ¹⁴C-uridine by LPS-stimulated LC's was inhibited by about 50% in the presence of infectious FV, whereas uptake in Con A-stimulated LC's was not inhibited. The inhibition of LPS stimulation was not detectable until 24 hr and later; the uptake of ³H-thymidine during the first 12 hr after infection and mitogen activation were the same in infected and noninfected cultures. The results indicate that MuLV-Friend infects normal B cells but that subsequent virus replication and secondary infection remain low unless the cells are activated with a mitogen. Virus replication, however, eventually becomes independent of cellular DNA synthesis, and the virus itself inhibits cellular nucleic acid synthesis at a later stage in the infection. (37 refs)

- 79-1576 Changes in the Transplantability of a Virus-induced Murine Leukemia Tumor.** (Eng) Portis, J. L. (Rocky Mountain Lab., Natl. Inst. Allergy and Infectious Diseases, NIH, Hamilton, MT, 59840). *J Natl Cancer Inst* 62(3): 611-617; 1979.

A study was made of the unstable sc growth potential (GP) of a Friend virus-induced murine leukemia cell line (FBL-3) passaged in ascites form. The GP was found to change, depending on the interval of time spent in the peritoneal cavity. Sc injection of the original stock of FBL-3 (grown continuously in vitro) into C56BL/10 mice produced transient tumors that were uniformly rejected by days 20-40. The tumor cells passaged in ascites form for 7 days behaved like the in vitro-grown cells, whereas ascites cells harvested at 14 days produced progressive lethal sc tumors in 50%-70% of the recipients. The results were similar in C57BL/6 mice. The change in sc growth was reversible simply by altering the ascites passage schedule. Day 7 ascites cells (regressors) were converted to progressors by ip passage for 14 days, and day 14 ascites cells (progressors) were converted to regressors by ip passage for 7 days. The difference in GP between day 7 and day 14 ascites cells was not due to effects of nonneoplastic host cells accompanying the tumor cells in the ascites population, because neither dilution of nonneoplastic cells by in vitro culture nor selective killing of *H-2a/b* host cells by anti-*H-2* serum and complement altered the sc growth behavior of either day 7 or day 14 ascites cells. These results indicate that the change in the GP of FBL-3 occurred at the level of the tumor cells. However, no quantitative differences were observed in the expression of serologically detectable tumor-associated antigens by these two populations. Possible mechanisms for this change in transplantability are considered. (14 refs)

- 79-1577 Identification of a Non-*H-2* Gene (*Rfv-3*) Influencing Recovery from Viremia and Leukemia induced by Friend Virus Complex.** (Eng) Chesebro, B. (Rocky Mountain Lab., Natl. Inst. Allergy and Infectious Diseases, Hamilton, MT, 59840); Wehrly, K. *Proc Natl Acad Sci USA* 76(1): 425-429; 1979.

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Two congenic backcross mouse generations (B10.A x A/WySn)_{F₁} x A/WySn and (C57BL/10 x A.BY)_{F₁} x A.BY, in which genes other than *H-2* were segregating, were examined to study recovery from Friend virus complex (FV) viremia independently of the *H-2* effect on recovery from leukemia. The dominant C57BL/10 allele of a single, autosomal, non-*H-2* gene (*Rfv-3*) was found to be required for recovery from viremia and leukemia induced by FV in *H-2b/b* mice. In *H-2a/a* mice, the *Rfv-3* gene apparently influenced recovery from viremia in the presence of persistent leukemia, because these mice lacked the appropriate *H-2* genotype for recovery from leukemia. The *Rfv-3* gene was distinct from the *Fv-2* gene, because recovery from viremia was seen in recombinant-inbred mice with the *Fv-2s/s* genotype. Furthermore, backcross studies indicated that *Rfv-3* and *Fv-2* were not linked. The *Rfv-3* gene may act by influencing the specific anti-FV humoral antibody response. (28 refs)

79-1578 Macrophage Accumulation Inhibited by Extracts of Murine Leukemia Viruses (MLV) (Meeting Abstract). (Eng) Cianciolo, G. J. (Howard Hughes Medical Inst., Duke Univ., Durham, NC, 27710); Thiel, H. J.; Bolognesi, D. P.; Snyderman, R. *Fed Proc* 38(3, part 2): 1364; 1979. (no refs)

79-1579 Antigenic Modulation of Virus-induced Lymphoma Cells In Vitro. (Eng) Sabbath, M. (Columbia Univ., New York, NY). *Diss Abstr Int B* 39(8): 3754; 1979. (no refs)

79-1580 Thrombocytic Reactions in Experimentally Induced Neoplasms. (Ger) Fey, F. (Zentralinstitut für Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany). *Arch Geschwulstforsch* 48(8): 705-711; 1978.

Strain XVII mice with various hematological types of Graffi virus-induced leukemia showed a pronounced thrombocytopenia (TCP) that was severe in the erythroblastic type and milder in the lymphatic types. The thrombocytic reactions that shortly followed Friend and Rauscher virus infection and occurred 3 wk after birth in AKR mice were not found with the the Graffi virus. A significant preleukemic TCP occurred 8 wk after Graffi virus infection in AKR mice. In neonatal (XVII x AKR)_{F₁} hybrids treated with N-nitroso-N-methylurea (NMU), the number of thrombocytes declined after manifestation of leukemia. An unexpected preleukemic TCP similar to that following viral leukemogenesis developed after NMU treatment. The possible cooperation of oncogenic viruses in chemical carcinogenesis is considered. (14 refs)

79-1581 Presence of Non-'Gag', Non-'Pol' Sequences in Rauscher Murine Leukemia Virus Pr200. (Meeting Abstract). (Eng) Kopchick, J. J. (Univ. Texas Sys-

tem Cancer Center, M. D. Anderson Hosp., Houston, TX, 77030); Karshin, W. L.; Arlinghaus, R. B. *Fed Proc* 38(3, part 1): 813; 1979. (no refs)

79-1582 Analysis of the Changes in Growth Fraction, Nuclear DNA Polymerase and Primer Template Levels During Rauscher Viral Leukemogenesis in Mice (Meeting Abstract). (Eng) O'Kunewick, J. P. (Cancer Res. Unit, Allegheny General Hosp., Pittsburgh, PA, 15212); Braunschweiler, P. G.; Meredith, R. F. *Cell Tissue Kinet* 11(6): 686-687; 1978. (no refs)

79-1583 Immunocytochemical Localization of gp70 over Virus-related Submembranous Densities in ts Mutant Rauscher Murine Leukemia Virus-infected Cells at the Nonpermissive Temperature. (Eng) Yeager, H. (Dept. Anatomy (Histology), Univ. Toronto, Toronto, Ontario, Canada M5S 1A8); Kalnins, V. I. *Virology* 91(2): 489-492; 1978.

An indirect immunocytochemical labeling technique employing goat antibody bound to colloidal gold particles as a marker was used to study the distribution of the major viral glycoprotein gp70 on surfaces of NIH/3T3 cells and virus in cultures infected with wild-type and mutant *ts29* Rauscher murine leukemia virus. When *ts29*-infected cells grown at the nonpermissive temperature (37°C) were treated with goat anti-gp70, the cell membranes over the submembranous densities were heavily labeled. When these cultures were shifted to a lower temperature, the amount of submembranous density was markedly reduced and a large number of early budding virus particles appeared. These particles also showed heavy labeling after treatment with goat anti-gp70. Relatively few gold particles were found over areas where submembranous densities or budding virions were absent, although the degree of labeling was above that seen in similar cultures treated with normal goat serum. The findings are consistent with the view that structural protein-membrane-glycoprotein interactions are important in C-type virus assembly. (9 refs)

79-1584 Association of Mouse Major Histocompatibility and Rauscher Murine Leukaemia Virus Envelope Glycoprotein Antigens on Leukaemia Cells and Their Recognition by Syngeneic Virus-Immune-Cytotoxic T-Lymphocytes. (Eng) Zarling, D. A. (Immunobiology Res. Center, Univ. Wisconsin, 1150 University Ave., Madison, WI, 53706); Keshet, I.; Watson, A.; Bach, F. H. *Scand J Immunol* 8(6): 497-508; 1978.

The physical association between the Rauscher murine leukemia virus (R-MuLV) envelope glycoprotein gp70 and the serologically defined mouse major histocompatibility antigen (H-2D) on the surface of R-MuLV-transformed C57BL/6 (H-2b; RBL-5A) cells was studied. The H-2b and R-MuLV gp70 proteins were independently precipitated from detergent-solubilized RBL-5A membrane protein extracts by

R-MuLV and H-2b antisera. Patching and capping experiments indicated that H-2Db and MLV gp70 antigens on RBL-5A cells form a specific mobile unit and redistribute together, therefore having a close topological relationship on the plasma membrane. H-2Db antigens appeared to be specific target molecules from syngeneic R-MuLV-immune cytotoxic T lymphocytes. α H-2Db sera, but not α H-2Kb sera, were highly effective in blocking T-lymphocyte-mediated lysis of RBL-5A cells; high-titer α R-MuLV gp70 sera had no effect. (32 refs)

- 79-1585 Murine Leukemia Virus gag Polyproteins: The Peptide Chain Unique to Pr80 is Located at the Amino Terminus.** (Eng) Schultz, A. M. (Viral Oncology Program, Frederick Cancer Res. Center, Frederick, MD, 21501); Oroszlan, S. *Virology* 91(2): 481-486; 1978.

The gag gene-encoded precursor polyproteins Pr80gag and Pr65gag of Rauscher leukemia virus were analyzed by chemical fragmentation, by immune precipitation with antisera specific to viral structural proteins, and then by one-dimensional peptide mapping. Cyanogen bromide fragmentation yielded two fragments common to both polypeptides: a fragment of 16,000-18,000 daltons (16K-18K); and a fragment of 46K. A fragment of 18K-20K occurred only in Pr65gag, and another peptide of 32K-34K was found only in Pr80gag. Fragmentation with 70% formic acid without cyanogen bromide yielded one major fragment of 46K common to both polyproteins, a fragment of approx 20K from Pr65gag, and a fragment of 33K from Pr80gag. The results suggest that Pr80gag is composed of Pr65gag and a 13K-15K peptide chain attached to the amino-terminus of Pr65gag. The carboxyl ends of the two polyproteins may be identical. (19 refs)

- 79-1586 A Murine Leukemia Virus Mutant with a Temperature-sensitive Defect in Membrane Glycoprotein Synthesis.** (Eng) Ruta, M. (Dept. Biochemistry, Sch. Medicine, Univ. Oregon Health Sciences Center, Portland, OR, 97201); Murray, M. J.; Webb, M. C.; Kabat, D. *Cell* 16(1): 77-88; 1979.

NIH/3T3 mouse cells infected with a temperature-sensitive mutant (ts-26) of Rauscher murine leukemia virus (R-MuLV) or with wild-type virus were labeled with 35 S-methionine, and cell extracts were examined for radioactive polypeptides by precipitation with monospecific antisera to viral proteins. When shifted from the permissive (31 C) to the nonpermissive (39 C) temperature, cells infected with ts-26 rapidly accumulated gPr90env, the glycoprotein precursor to the membrane envelope glycoprotein gp70 and to the membrane-associated protein p15E. At the same time, formation of these mature virion proteins stopped. Lactoperoxidase-catalyzed surface labeling with 125 I-iodine indicated that the plasma membrane of ts-26-infected cells became depleted of gp70 at 39 C. However, at 39 C these cells released defective MuLV's that lacked gp70 and p15E but contained an outer membrane. The released particles also contained an

aberrantly processed form of the major virion core protein p30. Many of these virion cores had an unusual immature, crescent shape. A previous report that cells infected with ts-26 process a 65,000-dalton precursor (Pr65gag) of the virion core proteins more slowly at 39 C than do cells infected with wild-type virus was confirmed, but the effect is relatively small. The amount of Pr65gag was approx 1.7 times higher in ts-26-infected cells than in wild-type virus-infected cells, whereas the concentration of fully processed p30 was reduced severalfold. It is proposed that a primary temperature-sensitive mutation in ts-26 occurs in its env gene and that the defect in Pr65gag processing is probably a secondary consequence of altered virion morphogenesis. (66 refs)

- 79-1587 Chemical Characterization of Rauscher Leukemia Virus Proteins.** (Eng) Brouwer, J. (Pathology Lab., State Univ. Leiden, Wassenaarseweg 62, Leiden, Netherlands); Pluijms, W. J.; Warnaar, S. O. *J Gen Virol* 42(2): 415-421; 1979.

Rauscher murine leukemia virus (R-MuLV) proteins were characterized by amino acid (AA) analyses and by mol wt determinations using gel filtration on cross-linked Sepharose 6B in 6 M guanidine HCl, and the results were compared with those for Moloney MuLV (M-MuLV) proteins. Two methods were used to isolate the proteins. When they were extracted from pelleted R-MuLV with buffer containing 0.4 M KCl and 1% Nonidet P40, 99.5% of the total protein was solubilized. Upon gel filtration, proteins gp70, p30, p15, and p12 were recovered as homogeneous fractions; the fraction containing p10 was slightly contaminated with p12. The chromatographic pattern obtained by gel filtration of a sample containing all the material present in a preparation of R-MuLV, including lipid and nucleic acid (method 2), was similar except that a homogeneous fraction of p10 was also obtained and contaminating proteins were present in the gp70 fraction. Mol wts of 56,000, 29,000, 15,000, 10,500, and 7,600 were found for gp70, p30, p15, p12, and p10, respectively. The two preparations of each protein gave identical results upon AA analysis. The sum of the percentages of met, phe, cys, leu, ile, val, trp, and his was taken as an index of hydrophobicity (HPB), and the order of HPB was p12E > 15, gp70 > p30 > p12, p10. p15 was the most hydrophobic of the gag gene-coded proteins. The AA compositions of the p10 and p30 polypeptides of R-MuLV and M-MuLV were very similar; the AA compositions of the p15 polypeptides were also similar, but not to the same extent. In contrast, the AA compositions of the p12 polypeptides differed considerably. These findings are expected from immunological data. (29 refs)

- 79-1588 Subcellular Distribution of Newly Synthesized Virus-specific Polypeptides in Moloney Murine Leukemia Virus-infected Cells.** (Eng) Shanmugam, G. (Dept. Biochemistry, Madurai Univ. Sch. Biological Sciences, Madurai 625021, India). *J Virol* 29(1): 385-389; 1979.

The newly synthesized virus-specific proteins present in the microsomal and postmicrosomal supernatant fractions of Moloney murine leukemia virus (MLV)-infected high-passage Swiss mouse embryo cells were studied by immune precipitation techniques. Anti-p30 serum precipitated five polypeptides (Pr88-gag, Pr72-gag, Pr62-gag, Pr39-gag, and p30) and anti-gp70 serum precipitated one polypeptide, Pr84-env. Most of the gag gene products were distributed in similar amounts in the microsomal and postmicrosomal supernatant fractions, whereas the envelope gene products were present predominantly in the microsomal fraction. A major proportion of p30 and its precursor intermediate Pr39-gag were also associated with the microsomal fraction. The data are consistent with the notion that the microsomal membrane fraction may play an important role in the replication of RNA tumor viruses. (25 refs)

- 79-1589 Antigenic Specificities of the Cellular Immune Response of C57BL/6 Mice to the Moloney Leukemia/Sarcoma Virus Complex.** (Eng) Enjuanes, L. (Cancer Biology Program, NCI Frederick Cancer Res. Center, Frederick, MD, 21501); Lee, J. C.; Ihle, J. N. *J Immunol* 122(2): 665-674; 1979.

The antigenic specificities of the cellular immune response against Moloney murine leukemia helper virus-Moloney sarcoma virus (MoLV-MSV)-induced tumors in C57BL/6 mice were studied using a variety of purified MoLV proteins. T-cell proliferation was directed primarily against the MoLV envelope glycoprotein gp71 and to a lesser extent against the MoLV protein p12. No blastogenic responses were detected against p10, p15, or p30. Blastogenesis was dependent on the presence of T cells but not rigidly dependent upon the presence of macrophages. There was no correlation in the relative magnitude of responses of individual mice to gp71 and p12. In microcytotoxicity assays using transformed nonproducer and producer cell lines with various virus serotypes. T-cell-mediated cytotoxicity in MoLV-MSV-infected mice was directed against MoLV gp71 and was not associated with the defective transforming virus. Antigen blocking experiments demonstrated that only MoLV gp71 could significantly block cytotoxicity (> 80%), which suggests that the major cytotoxic response was directed against MoLV gp71. Cell-mediated cytotoxicity was 10-12 days postinoculation, after the tumor had reached its peak size, and was no longer detectable by 25 days, when the tumor had regressed. The blastogenic response was biphasic: the first peak in reactivity was roughly comparable to the cytotoxicity pattern; the second peak was approx 50 days, after which it slowly declined. (29 refs)

- 79-1590 A Defined Subgenomic Fragment of In Vitro Synthesized Moloney Sarcoma Virus DNA Can Induce Cell Transformation upon Transfection.** (Eng) Andersson, P. (Fibiger Lab., DK-2100 Copenhagen 0, Denmark); Goldfarb, M. P.; Weinberg, R. A. *Cell* 16(1): 63-75; 1979.

DNA was synthesized in vitro by endogenous reverse transcription in detergent-permeabilized Moloney murine sarcoma virus (Mo-MSV) virions [clone G8-124, which contains a minimum of helper Moloney murine leukemia virus (Mo-MLV)]. In the absence of actinomycin D, the longest DNA molecules synthesized were double-stranded DNA (dsDNA) molecules of 5.8 kilobase pairs (kbp). A physical map of the positions of the cleavage sites for a series of restriction endonucleases was derived for this 5.8-kbp DNA after purification through neutral sucrose gradients. Mo-MSV DNA synthesized in vitro induced morphological transformation of MLV-infected and uninfected NIH-3T3 mouse fibroblasts upon transfection. The foci had a morphology indistinguishable from that of Mo-MSV-induced foci, and the induced transformed phenotype was stable. Gel-purified, restriction endonuclease-generated fragments of 5.8-kbp dsDNA containing the region from 2.8 to 4.9 kbp on the physical map of Mo-MSV DNA also induced foci, but endonuclease-generated DNA fragments lacking this region did not. When transformants derived by transfection with 5.8-kbp dsDNA were infected with Mo-MLV helper virus, Mo-MSV was rescued from a small portion of these cells, suggesting the establishment of the complete viral genome. The Mo-MSV DNA fragment spanning 2.8-4.9 kbp on the physical map represents the max estimate for the size of the transforming region of the Mo-MSV genome. This fragment includes the Mo-MSV sequences that are found in the DNA of uninfected mouse cells. It is speculated that the transforming function of Mo-MSV may be specified by nucleotide sequences that are totally of mouse cell or endogenous viral origin. (36 refs)

- 79-1591 Immunologic Regulation of Virally-induced Leukemogenesis by the Thymus (Meeting Abstract).** (Eng) Reinisch, C. L. (Div. Tumor Immunology, Sidney Farber Cancer Inst., Boston, MA, 02115); Kurtz, S. *Fed Proc* 38(3, part 2): 1466; 1979. (no refs)

- 79-1592 Role of Glycoconjugates in Expression of the Transformed Phenotype.** (Eng) Steiner, S. (Dept. Virology, Baylor Coll. Medicine, Houston, TX, 77030); Via, D.; Klinger, M.; Larriba, G.; Sramek, S.; Laine, R. *ACS Symposium Series* 80: 378-403; 1978.

Changes in fucose metabolism in murine sarcoma virus-transformed cells compared with that in normal cells were studied. These studies initially focused on the low-mol-wt, organic-extractable fucosylated components. The aminoacyl fucosides have been observed in all normal mammalian cell lines thus far examined. These components, FL3a (threonine and fucose), FL3b (serine and fucose), FL4a (threonine, fucose, and glucose) and FL4b (serine, fucose and glucose), appear to be a novel series of compounds with fucose O-glycosidically linked to amino acid. Glucose appears to be the terminal sugar in FL4a. There was a marked decrease in the incorporation of radioisotopically labeled fucose into FL4a in a variety of oncogenically transformed cells. The level of FL4a also

appeared to vary as a function of the expression of the transformed morphological phenotype. There was a glycoprotein(s) in which fucose appeared to be O-glycosidically linked to amino acid. The results of pulse studies with ^3H -fucose were consistent with the fucoprotein(s) being a precursor of FL4a. (19 refs)

- 79-1593 Revertants of Mouse Cells Transformed by Murine Sarcoma Virus. V. Loss of MSV-Specific Nucleotide Sequences from Cellular RNA.** (Eng) Nomura, S. (Lab. Viral Carcinogenesis, NCI, Bethesda, MD, 20014). *Virology* 91(2): 444-452; 1978.

To investigate the mechanism of reversion in Moloney murine sarcoma virus (M-MSV)-transformed 3T3 cells [sarcoma-positive, leukemia-negative (S+L-) cells], cellular RNA and DNA were hybridized with total complementary DNA (cDNA) or MSV-specific cDNA derived from the M-MSV genome. Two types of revertants were obtained: flat, S- (rescue-negative), p30-positive revertants and a morphological revertant that differed from the parental cells only in that it was flat. Murine leukemia virus (MuLV) p30 determinants were expressed in most revertants, and the S+L- revertant cellular RNA's hybridized with unfractionated MSV (feline leukemia virus) cDNA. Using MSV-specific cDNA, it was demonstrated that MSV-specific viral RNA was absent from the S- revertants. However, the sequences homologous to MSV-specific cDNA were found in all revertant cellular DNA's, and they were quantitatively and qualitatively indistinguishable from those in the parental S+L- cells. The data indicate that only cells that retained rescuable MSV genomes contained MSV-specific viral RNA, irrespective of the cellular phenotype. By inference, sequences common to M-MSV and M-MuLV viral RNA contained at least part of the *gag* gene. M-MSV-specific nucleotide sequences were present, however, in DNA's both from revertants and S+L- cells, suggesting that either restriction in transcription of the viral genome or in processing of viral RNA sequences is responsible for S- revertants from S+L- cells. (41 refs)

- 79-1594 Studies of a Large Transformation-increased Membrane Protein in the BHK21 Cell System.** (Eng) Lage-Davila, A. (Instituto Nacional de Oncologia y Radiobiologia, 29 y E Vedado, Havana, Cuba); Montagnier, L. *Biochim Biophys Acta* 550(3): 435-449; 1979.

A 177,000-dalton (177K) plasma membrane protein that is significantly increased in baby hamster kidney (BHK21/13) cells transformed by hamster sarcoma virus was characterized by solubilization, cross-linking, metabolic labeling, and enzymatic radioiodination experiments. Electrophoretic analysis of the plasma membrane fractions from both transformed and untransformed BHK cells revealed a set of 18 major polypeptides (mol wt 50K-300K) whose presence and relative proportions were highly reproducible. The data showed that the 177K protein is: (1) a product of cellular metabolism because it could be labeled with ^{35}S -methionine;

(2) a membrane protein because it copurified with known plasma membrane fractions and with external iodine label; (3) probably a glycoprotein because it comigrated with a ^{14}C -glucosamine band upon gel electrophoresis; (4) partially exposed, because it could be iodinated externally by the non-penetrating lactoperoxidase reaction and because this label was trypsin-sensitive; and (5) an integral membrane protein, because it could only be solubilized in the presence of detergents and SH-reducing agents. The protein could be cross-linked and made to disappear rapidly from electrophoretograms after SH oxidation catalyzed by o-phenanthroline- CuSO_4 , which indicates that it is probably an SH-containing protein. Thus, 177K can be characterized as an integral membrane glycoprotein that is partially exposed at the outer cell surface. Data on several other membrane proteins of untransformed and transformed BHK cells are included. (19 refs)

- 79-1595 Evidence for Antigenic Determinants Shared by the Structural Polypeptides of (Shope) Rabbit Papillomavirus and Human Papillomavirus Type 1.** (Eng) Orth, G. (Unite de Recherches sur l'Étiologie Virale des Cancers Humains, Institut Gustave-Roussy, 94800, Villejuif, France); Breitburd, F.; Favre, M. *Virology* 91(2): 243-255; 1978.

Sera containing anti-(Shope) rabbit papillomavirus (RPV) antibodies were collected from 10 Vx7 carcinoma-bearing rabbits and used to study common antigenic determinants on RPV and human plantar wart papillomavirus type 1 (HPV-1). Seven of the 10 sera gave positive staining when tested by indirect immunofluorescence on human plantar wart sections. Staining with fluorescein-conjugated IgG from the serum with the highest antibody titer (Vx7-R221) showed that cross-reacting antigens were localized in the nuclei of the keratinizing cells and in keratinized cells in which HPV-1 capsid antigens were detected in an adjacent section using fluorescein-conjugated anti-HPV-1 virion IgG. The amount of cross-reacting antigen was lower than that of viral capsid antigen. For Vx7-R221 serum, cross-reacting antibodies were raised against an antigenic determinant(s) borne by viral structural polypeptides and masked in intact particles. Vx7-R221 serum precipitated mainly the 54,000-dalton HPV-1 polypeptide; ie, the capsomere subunit. Anti HPV-1 polypeptide sera contained antibodies against both HPV-1 antigens and RPV antigens, as detected by immunofluorescence. One of the cross-reactive Vx7 sera (Vx7-R337) gave a precipitin line continuous with that given by an anti-HPV-1 virion antiserum when tested by immunodiffusion using HPV-1 virions as antigens. This was also observed with 4/110 additional Vx7 sera tested. The results indicate that two kinds of antigenic determinants are shared by RPV and HPV-1 structural polypeptides: some are masked in intact particles and others are located on the virion surface but in a form usually unable to elicit antibody formation. (43 refs)

- 79-1596 Induction of Virus-associated Tumors in Carcinogen-treated Guinea Pigs (Meeting Ab-**

stract). (Eng) Lubiniecki, A. S. (Melo Lab., Inc., Springfield, VA, 22151); Szakal, A. K. *Fed Proc* 38(3, part 2): 1450; 1979. (no refs)

79-1597 Morphological Evidence for the Presence of the Endogenous Guinea-Pig Retrovirus in the Lymphoblasts of L2C Leukemia. (Eng) Perk, K. (Dept. Animal Science, Hebrew Univ. Jerusalem, Rehovot Campus, P.O.B. 12, Rehovot, Israel); Dahlberg, J. E. *Experientia* 35(1): 104-105; 1979.

Blood samples from guinea pigs with L2C leukemia were examined for guinea pig virus (GPV) particles. Only during the terminal stages of the disease did L2C leukemic cells show virus particles indistinguishable from tissue-cultured GPV. Extracellular virus particles and intracytoplasmic A particles were frequently observed, but budding particles were rare. All of the budding particles observed contained completely formed nucleoids. The morphologic evidence for the presence of a B-type retrovirus in the late stages of leukemogenesis indicates that a positive correlation exists between the morphologically complete expression of endogenous virus genes in L2C leukemic cells and malignancy, particularly leukemia, in guinea pigs. (23 refs)

79-1598 Development of Early Lesions in Cats with Experimental Ocular Melanoma (Meeting Abstract). (Eng) Shaddock, J. A. (Univ. Texas Health Science Center at Dallas, Dallas, TX, 75235); Albert, D. *Fed Proc* 38(3, part 2): 1270; 1979. (no refs)

79-1599 Biological Properties and Translational Products of Three Independent Isolates of Feline Sarcoma Virus. (Eng) Porzig, K. J. (Lab. Cellular and Molecular Biology, NCI, Bethesda, MD, 20014); Barbacid, M.; Aaronson, S. A. *Virology* 92(1): 91-107; 1979.

The biological properties and translational products of three transforming strains of feline sarcoma virus (FeSV), SM, GA, and ST, were characterized. The three retroviruses were isolated independently from naturally occurring tumors of outbred cats. Like previous mammalian transforming viruses, each FeSV strain was demonstrated to be replication-defective, requiring a C-type RNA virus as a helper. Reproducible differences were demonstrated in the morphology of transformed foci induced by each FeSV strain. These findings were independent of helper virus or assay cell utilized, suggesting that the transforming activities of the three FeSV strains are distinguishable. Nonproducer transformants of SM-FeSV expressed the feline leukemia virus (FeLV) *gag* gene products p15, p12, and p30. In contrast, the GA- and ST-FeSV genomes coded only for p15 and p12 proteins, further distinguishing SM-FeSV from the other FeSV strains. Each remained stable with respect to viral protein expression upon transmission to new cells, demonstrating the stable association of FeLV *gag* gene information with each FeSV genome.

Analysis of the FeLV structural proteins translated in non-producer transformants of the three FeSV strains revealed the presence of precursor molecules whose sizes could not be accounted for solely by the number of FeLV *gag* proteins present in them. (43 refs)

79-1600 Antibody Response in Cats to Feline Leukemia Virus Reverse Transcriptase under Natural Conditions of Exposure to the Virus. (Eng) Jacquemin, P. C. (Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20014); Saxinger, C.; Gallo, R. C.; Hardy, W. D.; Essex, M. *Virology* 91(2): 472-476; 1978.

The sera of feline leukemia virus (FeLV)-exposed, feline sarcoma virus (FeSV)-exposed, and unexposed cats were examined for the presence of natural antibodies to reverse transcriptase (RT). The 68 animals studied belonged to one of five groups: (A) specific pathogen-free cats known to be unexposed to FeLV and FeSV; (B) randomly collected healthy street cats; (C) household cats known to have been exposed to FeLV under natural conditions; (D) cats with pathologically confirmed cases of lymphoma or lymphoid leukemia acquired under natural conditions; and (E) specific pathogen-free cats injected with their own cells that had been infected in the laboratory with FeLV or FeSV. Antibodies to RT were detected only in nonviremic cats. All sera with anti-RT activity also contained antibody to feline oncornavirus membrane-associated antigen (FOCMA), but sera from 2 Group B cats, 5 Group C cats, and 1 Group E cat contained moderate or high levels of anti-FOCMA without neutralizing activity for FeLV RT. The results of an assay for neutralization of RT functional activity suggested that RT antibody activities were sometimes discordant from those directed to FOCMA. (33 refs)

79-1601 Feline Leukemia Virus: Survival Under Home and Laboratory Conditions. (Eng) Francis, D. P. (Dept. Microbiology, Harvard Sch. Public Health, Boston, MA, 02115); Essex, M.; Gayzagian, D. *J Clin Microbiol* 9(1): 154-156; 1979.

The stability of feline leukemia virus (FeLV) released into the environment was studied. The studies included salivary FeLV survival on a dry surface similar to surfaces found in homes and FeLV survival in laboratory culture medium to simulate conditions in research laboratories. Titers of infectious salivary FeLV dropped rapidly in saliva that was allowed to dry on glass cover slips at room temperature. Loss of infectious virus was also observed when FeLV from a non-saliva source was allowed to dry. Levels of infectious FeLV in media dropped to < 10 infectious units within 60 min after drying. Cell-free FeLV in cell culture medium was stable at temperatures from 4 to 37 C, but there was a rapid (within 3-4 hr) loss of infectiousness at 56 C. Although the infectiousness of salivary FeLV declined relatively rapidly on dry surfaces, the 30- to 60-min interval during which significant FeLV could still be detected might be adequate to transfer

the agent. The relative stability of FeLV suggests that transmission could also occur through the sharing of common food and water containers. Owners of infected pet cats might also be exposed to high levels of FeLV depending on their interactions with their cats, and the potential for human infection in the laboratory seems considerable. (16 refs)

79-1602 Activation of Feline Complement by Feline Leukemia Virus (Meeting Abstract). (Eng) Kobinsky, L. (Sloan-Kettering Inst. for Cancer Res., New York, NY, 10021); Hardy, W. D.; Ellis, R.; Day, N. K. *Fed Proc* 38(3, part 2): 1010; 1979. (no refs)

79-1603 Induction of C-Type Virus in Cell Lines Derived from Calf Form Bovine Lymphosarcoma. (Eng) Onuma, M. (Dept. Epizootiology, Faculty Veterinary Medicine, Hokkaido Univ., Sapporo 060, Japan); Okada, K.; Yamazaki, Y.; Fujinaga, K.; Fujimoto, Y.; Mikami, T. *Microbiol Immunol* 22(11): 683-691; 1978.

Serologic tests, electron microscopy, and a reverse transcriptase assay were used to study the induction of C-type virus by 5'-iodo-2-deoxyuridine (IUdR) and glucocorticoid dexamethasone (DXM) in cell cultures derived from adult form (ALS), calf form (CLS), and thymic form (TLS) bovine lymphosarcoma. Bovine leukemia virus (BLV) antigen was consistently detected in untreated ALS 3153 and 3169 cultures but not in any of the other untreated cultures. BLV particles were also detected in untreated ALS 3169, and a few were detected in CLS 3182, but none were found in any of the other untreated cultures. After treatment with IUdR or DXM, BLV antigen and BLV particles were detectable in CLS 3178 cells which changed from a epithelioidlike to a fibroblastlike morphology and began proliferating rapidly. The reverse transcriptase assay was positive for ALS 3153 and CLS 3178. The other cultures remained negative for virus antigen, particles, and reverse transcriptase after chemical treatment. (26 refs)

79-1604 Structure of the Genome of Equine Herpesvirus Type 1 (Meeting Abstract). (Eng) Henry, B. E. (Univ. Mississippi Medical Center, Jackson, MS); Hayward, G. S.; Dauenhauer, S. D.; O'Callaghan, D. J. *Fed Proc* 38(3, part 1): 814; 1979. (no refs)

79-1605 Purification and Biochemical Characterization of Deoxythymidine Kinase (dTK) of Deoxythymidine Kinase Deficient Mouse 3T3 Cells Biochemically Transformed by Equine Herpesvirus Type 1 (Meeting Abstract). (Eng) McGowan, J. J. (Univ. Mississippi Medical Center, Jackson, MS, 39216); Allen, G. P.; Gentry, G. A. *Fed Proc* 38(3, part 2): 1403; 1979. (no refs)

79-1606 Immunological Relatedness of Papillomaviruses from Different Species (Meeting Abstract).

(Eng) Shah, K. (Johns Hopkins Univ., Baltimore, MD); Jenson, A. B.; Pass, F.; Lancaster, W. D.; Olson, C. *Fed Proc* 38(3, part 2): 1070; 1979. (no refs)

79-1607 Cholesterol Content and Metabolism in Normal and Polyoma Virus-transformed Hamster Embryo Fibroblasts. (Eng) Mark-Malchoff, D. (Dept. Biochemistry, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY, 14642); Marinetti, G. V.; Hare, J. D.; Meisler, A. *Exp Cell Res* 118(2): 377-381; 1979.

Free and esterified cholesterol (CE) levels were determined by thin-layer chromatography in normal hamster embryo fibroblasts (HEF) and their polyoma virus-transformed counterparts (HFT). The total CE level was 6.8 and 6.6 $\mu\text{g}/10^6$ cells in HEF and HFT cells, respectively. However, the free CE level was 6.6 $\mu\text{g}/10^6$ HEF cells and 4.2 $\mu\text{g}/10^6$ HFT cells, but that of esterified CE was 0.2 $\mu\text{g}/10^6$ HEF cells and 2.4 $\mu\text{g}/10^6$ HFT cells. Thus, the free CE:CE ester ratio was 41.5 in normal cells and 1.8 in the transformed cells. CE uptake was 995 picomoles (pmol)/ 10^6 HEF cells/hr compared with 625 pmol/ 10^6 HFT cells/hr. The normal cells also took up more CE oleate than their transformed counterparts. However, the esterification of CE was higher and the hydrolysis of CE oleate was lower in HFT cells. This partly explains the difference in the free CE:CE ratio between the normal and transformed cells. The significance of the altered lipid composition of HFT cells may be related to the enhanced uptake of nutrients by these cells, possibly conferring on them an advantage for growth. (39 refs)

79-1608 Studies on Polyoma Virus DNA Replication in Synchronized C3H2K Cells. (Eng) Loche, M. P. (Fondation Curie-Institut du Radium, 15, rue Georges Clemenceau, Batiment 110, 91405 Orsay, France). *J Gen Virol* 42(2): 429-433; 1979.

The temporal relationship between polyoma virus DNA synthesis (VDS) and cellular DNA synthesis (CDS) was studied in C3H2K mouse kidney fibroblasts arrested in G_1 and infected at different times after serum stimulation (SS) to progress to the S phase. CDS was measured by ^3H -thymidine pulse-labeling and cell counts. VDS was determined by DNA infectivity titrations using plaque-purified virus and by isolating virus DNA form I on equilibrium density gradients. Both methods gave almost identical results with respect to the kinetics of VDS. VDS was max in the middle of the S phase, and VDS and CDS proceeded almost synchronously. VDS was only slightly delayed in cells infected up to 12 hr after SS, compared with cells infected immediately after SS. However, when cells were infected > 13 hr after SS, when they had already entered the S phase, VDS was delayed until the next S phase. Apparently, the early virus information needed to initiate viral DNA replication must be expressed before a critical period of the S phase is attained. The similar yields and kinetics of VDS recorded in cells infected before and 12 hr after SS indicate that SS factors can efficiently replace the

early virus host DNA stimulation function. When cells were incubated in serum that had lost its capacity to stimulate host DNA synthesis by preabsorption with growing cells, normal yields of polyoma DNA were still obtained, which shows that extensive replication of host DNA is not obligatory for virus DNA replication. (23 refs)

79-1609 RNA Hybridization to DNA Coupled with Cyanogen-Bromide-activated Sephadex: The Purification of Polyoma Messenger RNA. (Eng) Siddell, S. G. (Institut für Virologie und Immunbiologie, Justus-Maximilians-Universität Würzburg, Versbacher Landstrasse 7, D-8700 Würzburg, W. Germany). *Eur J Biochem* 92(2): 621-629; 1978.

A method for purifying RNA by hybridization to complementary DNA immobilized on cyanogen bromide-activated Sephadex is described and is illustrated by the purification of polyoma messenger RNA. It is necessary to elute RNA from DNA-Sephadex by a combination of formamide buffers containing NaCl and by elevated temperatures, conditions that dissociate DNA-RNA hybrids and also prevent the binding of RNA to the resin by ion exchange. (37 refs)

79-1610 Characterization of Simian Virus 40 Tumor Antigen from Nuclei and Purified Plasma Membranes of Transformed Cells (Meeting Abstract). (Eng) Soule, H. R. (Baylor Coll. Medicine, Houston, TX, 77030); Butel, J. S. *Fed Proc* 38(3, part 2): 1104; 1979. (no refs)

79-1611 Replication of SV40 Chromosome in a Subnuclear Fraction: Characterization of Viral Chromosome (Meeting Abstract). (Eng) Su, R. T. (Univ. Kansas, Lawrence, KS, 66045). *Fed Proc* 38(3, part 1): 812; 1979. (no refs)

79-1612 Additional SV40 Early Proteins in Infected CV-1 Cells (Meeting Abstract). (Eng) Yang, Y. C. (Northwestern Univ. Medical Center, Chicago, IL, 60611); Hearing, P.; Rundell, K. *Fed Proc* 38(3, part 1): 812; 1979. (no refs)

79-1613 Reactivation of a Silent Mouse rRNA Gene by SV-40-Human-Mouse Hybrid Cells (Meeting Abstract). (Eng) Soprano, K. J. (Temple Univ., Philadelphia, PA); Dev, V. G.; Croce, C.; Baserga, R. *Fed Proc* 38(3, part 1): 813; 1979. (no refs)

79-1614 Transformation In Vitro of Thyroid Cell Lines by Oncogenic Viruses (Meeting Abstract). (Eng) Tramontano, D. (Centro di Endocrinologia ed Oncologia Sperimentale del C.N.R., Istituto di Patologia Generale, II Facoltà di Medicina e Chirurgia, Naples I-80131, Ita-

ly); Ambesi-Impiombato, F. S. *Ann Endocrinol (Paris)* 39(5): 49A; 1978. (no refs)

79-1615 Effect of Treatment with SV40 Tumor Membrane Antigen Extract or Spleen Cells from Antigen Sensitized Hosts on Tumor Growth In Vivo (Meeting Abstract). (Eng) Prather, S. O. (Univ. Nebraska, Lincoln, NE, 68588); Lausch, R. N. *Fed Proc* 38(3, part 2): 1106; 1979. (no refs)

79-1616 Cytotoxicity to Shope Fibromas Virus in Infected Adult and Newborn Rabbits (Meeting Abstract). (Eng) Scott, C. B. (Univ. California at San Diego, La Jolla, CA, 92093); Holdbrook, R.; Sell, S. *Fed Proc* 38(3, part 2): 1364; 1979. (no refs)

79-1617 The Growth Stimulation of SV3T3 Cells by Transferrin and Its Dependence on Biotin. (Eng) Young, D. V. (Dept. Chemistry, Boston Univ., Boston, MA, 02215); Cox, F. W.; Chipman, S.; Hartman, S. C. *Exp Cell Res* 118(2): 410-414; 1979.

Studies were conducted to identify factors critical for the growth stimulation of SV3T3 cells, a virally transformed derivative of the mouse fibroblast cell line 3T3. Iron in the ferrous form or in the ferric state with a suitable complexing agent was identified as a critical nutrient for SV3T3 growth. Both Hb and transferrin were capable of stimulating SV3T3 proliferation in low-serum or serum-free biotin-supplemented medium. SV3T3 cells did not grow in serum-free medium without iron. Growth is restored, although not to the levels obtained with saturating calf serum, upon the radiation of ferrous sulfate, Hb, or transferrin. Biotin addition alone did not stimulate SV3T3 growth, but its presence was required for growth stimulation by ferrous sulfate, transferrin, or Hb. The reason for this dependence on biotin is not known. The results also indicate that in addition to biotin and transferrin, unidentified serum growth factors are still needed to maximize the initial growth rate of SV3T3 cells. (12 refs)

79-1618 Factors Affecting the Frequency of Transformation of Rat Embryo Cells by Simian Virus 40. (Eng) Risser, R. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706); Pollack, R. *Virology* 92(1): 82-90; 1979.

An earlier observation that simian virus 40 (SV40) induces distinct patterns of transformed behavior upon infection of primary rat cells was confirmed, and factors influencing their generation were explored. The transformation of primary Fischer rat embryo cells into established cell lines by SV40 was monitored by the different restrictive assays of colony formation in sparse culture, dense colony or focus formation on a confluent cell sheet, and colony formation in semisolid medium. The primary embryonic rat cell cultures were con-

siderably less susceptible to infection and subsequent transformation than the established mouse 3T3 cell line or later in vitro passages of rat cells. These embryonic cells showed a stage-specific susceptibility to transformation but not to infection, with max susceptibility being achieved on gestation days 15-16. All transformed cell lines derived from SV40 infection of primary rat cells expressed viral tumor (T) antigen, as detected by immunofluorescence, although they differed greatly in their plating efficiency in semisolid medium containing methylcellulose. Only the assay of colony formation in semisolid medium selected directly for transformants that plated well in that medium, but all assays appeared to select for cell lines containing viral T antigen. (32 refs)

- 79-1619 Deletion Mutants of Simian Virus 40 Defective in Biosynthesis of Late Viral mRNA.** (Eng) Lai, C. J. (Lab. Molecular Virology, NCI, NIH, Bethesda, MD, 20014); Khoury, G. *Proc Natl Acad Sci USA* 76(1): 71-75; 1979.

Simian virus 40 deletion mutants lacking sequences in the late genomic region were examined for genetic elements that control the biosynthesis of the viral messenger RNA's (mRNA's). Mutant-specific RNA from infected cells was identified by CH₃Hg(OH)/agarose gel electrophoresis and mapped by the nuclease S1 technique. Altered 16S or 16S + 19S RNA species, shortened by a size equivalent to the deletion region, could be detected in cells infected with mutants lacking sequences within the body RNA segments. On the other hand, mutants that lacked the 5' end of the body sequences (a splice junction) failed to accumulate the respective shortened RNA species. In particular, mutant dl-2301, whose deletion includes both the leader and body splice junctions plus the intervening sequences, exhibited a polar effect on a distal gene. Although the late region of dl-2301 could be transcribed normally, the mutant defect appeared to be associated with little or no accumulation of the mutant-specific late RNA in the infected cells. These results suggest that splice junctions and/or the intervening sequences in the viral genome are control signals for posttranscriptional processing of the viral RNA. (24 refs)

- 79-1620 Enhancement of Simian Virus 40 Uptake by Permissive, Semi-permissive and Non-permissive Cells.** (Eng) Tan, K. B. (Wistar Inst. Anatomy and Biology, 36th and Spruce Sts., Philadelphia, PA, 19104). *Cytobios* 20(79/80): 143-149; 1977.

Various reagents were tested for their ability to enhance simian virus 40 (SV40) uptake in permissive (monkey), semipermissive (human), and nonpermissive (mouse, chick, snake, and fish) cells. Arginine-rich histones and diethylaminoethanol (DEAE)-dextran markedly enhanced virus uptake in all three types of cells. Optimum enhancement of virus uptake occurred at a DEAE-dextran concentration of 100 µg/ml. Under the conditions tested, DEAE-dextran was not cytotoxic but the histones were. Nuclear uptake of virus was

rapid, with a 50% uptake occurring within 12-14 min for human and mouse cells and 20 min for monkey cells. The increased cellular uptake of virus may result from the uptake of virus aggregates formed in the presence of DEAE-dextran. (12 refs)

- 79-1621 Variant Lines of Mouse Kidney Cells Transformed by an SV40_{tsA} Mutant with Growth Properties of Wild-Type Transformed Cells at Nonpermissive Temperature.** (Eng) Otsuka, H. (Div. Biochemical Virology, Baylor Coll. Medicine, Houston, TX, 77030); Dubbs, D. R.; Kit, S. *J Gen Virol* 42(2): 373-386; 1979.

A BALB/c mouse kidney line (mKSA207) transformed by a *tsA* mutant of simian virus 40 (SV40) is temperature-dependent for expression of the "standard transformed phenotype." At the permissive temperature (33.5 C), the mKSA207 cells resembled wild-type (wt) SV40 transformants: they contained intranuclear SV40 tumor (T) antigen, grew to high saturation density in monolayer culture in either 10% or 0.5% serum and also in methylcellulose suspension culture (MCSC); and became multinucleate in cytochalasin B. At the nonpermissive temperature (39.8 C), the mKSA207 cells lost some of their transformed properties: they grew only to low density in 10% serum, hardly grew at all in 0.5% serum or in MCSC, and remained mono- or binucleate in cytochalasin B. At 40 C in low serum, mKSA207 cells lost the intranuclear T antigen, and when they were fed 10% serum at 39.8 C, they accumulated large amounts of T antigen in the cytoplasm. Derivatives of mKSA207 were selected at 39.8 C in liquid medium and in MCSC. The heat-adapted lines, like wt SV40 transformants, exhibited the standard transformed phenotype at both 33.5 and 39.8 C. It is unlikely that acquisition of temperature-independence for the transformed phenotype was due to reversion of the *tsA* gene to wild-type, because the heat-adapted cell lines displayed the cytoplasmic T antigen at 39.8 C, and SV40 rescued from one of the heat-adapted lines was temperature-sensitive for growth. The T-antigen levels (complement fixation units/10⁶ cells) of heat-adapted lines grown at 39.8 C were comparable to those of mKSA207 cells grown at 33.5 or 39.8 C. (37 refs)

- 79-1622 Establishment and Characterization of Indian Muntjak Cell Lines Transformed with Simian Virus 40.** (Eng) Yamaguchi, N. (Inst. Medical Science, Univ. Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108, Japan); Huh, N. *J Gen Virol* 42(2): 289-296; 1979.

The kidney cells of an Indian muntjak (*Muntiacus muntjak vaginalis*) were transformed with simian virus 40 (SV40). The transformation efficiency of the tertiary cultures was very high when estimated by the agar suspension culture method, being about 0.015% at an input multiplicity of 0.4 plaque-forming unit/cell. Clonal cell lines were established from the colonies in soft agar and characterized. SV40 tumor antigen was detected in the nuclei of nearly all the cells of any clone. Infectious SV40 was detected in all but one clone.

The yield of infectious SV40 was enhanced 30-fold and the percentage of virion antigen-positive cells in a clone was increased from 0.2% to 40% by treatment with mitomycin C. More than 70% of the cells in two cell lines had normal G- and C-banded karyotypes, indicating that chromosomal change is not a necessary step in the transformation of Indian muntjak cells with SV40. (30 refs)

79-1623 Evolutionary Variants of Simian Virus 40: Cellular DNA Sequences and Sequences at Recombinant Joints of Substituted Variants. (Eng) Gutai, M. W. (Dept. Viral Oncology, Roswell Park Memorial Inst., Buffalo, NY); Nathans, D. *J Mol Biol* 126(2): 275-288; 1978.

Cellular DNA and host-viral joints present in the recombinant genome of an evolutionary variant of simian virus 40 (SV40) were analyzed at the nucleotide sequence level. Cellular DNA segments were interspersed with viral DNA and were arranged in part as tandem sequence repetitions. Some of the cellular DNA was derived from highly repeated sequences of host cell DNA, and it corresponded to sequences found in other substituted SV40 variants. Ten recombinant host-viral joints were identified in the variant genome, six of which showed distinct nucleotide sequences on both sides of the joint. In all but one case, sequences about the joint were rich in clusters of A-T base pairs. In one case, joint sequences could be compared with both viral and cellular sequences from which they were derived: short interrupted stretches of homology with each parental sequence were detected. Of the five remaining joints, which could be compared only with the SV40 parental sequence, two showed patchy homology with SV40 sequences adjacent to the joint. It is concluded that recombination between SV40 and cellular DNA occurs at many different nucleotide sequence positions in both parental DNA's, that extensive nucleotide sequence homology is not required for such recombination, that discontinuous or patchy homology may play a role in this event, and that A-T clusters may increase the probability of recombination at a given site. (26 refs)

79-1624 Evolutionary Variants of Simian Virus 40: Nucleotide Sequence of a Conserved SV40 DNA Segment Containing the Origin of Viral DNA Replication as an Inverted Repetition. (Eng) Gutai, M. W. (Dept. Viral Oncology, Roswell Park Memorial Inst., Buffalo, NY); Nathans, D. *J Mol Biol* 126(2): 259-274; 1978.

The predominant evolutionary variant of simian virus 40 (SV40) was cloned from the 45th passage stock (BSC-1 cells) and its genome was analyzed by electron microscopy, restriction endonuclease cleavage, and nucleotide sequence determination. The variant genome consisted of SV40 DNA joined to cellular DNA, and it was made up of three tandemly arranged repeats of a basic DNA segment that was 28% of the length of wild-type SV40 DNA. Within each basic segment, the SV40 sequences derived from the region of the replication origin were present as an inverted repetition. There were 164

nucleotides of SV40 DNA on one side of the inverted sequence and 198 nucleotides on the other side. The variant sequence was the same as that found in parental SV40 DNA except for the presence of small tandem repeats within the variant segment. These data, combined with the results of other studies of SV40 variants and deletion mutants, localize the SV40 origin signal to a segment of DNA of about 80 nucleotides between map units 0.66 and 0.68. (44 refs)

79-1625 Heterogeneity and 5'-Terminal Structures of the Late RNAs of Simian Virus 40. (Eng) Ghosh, P. K. (Dept. Internal Medicine and Human Genetics, Yale Medical Sch., New Haven, CT, 06510); Reddy, V. B.; Swinscoe, J.; Lebowitz, P.; Weissman, S. M. *J Mol Biol* 126(4): 813-946; 1978.

The 5'-terminal structures of the late lytic RNA's of simian virus 40 (SV40) were studied by binding the plus strand of small DNA fragments labeled in the 5'-terminal position with ³²P to specific regions of cytoplasmic polyadenylated late RNA, extending these "primer" fragments in a 3' direction with reverse transcriptase, fractionating the extended products on denaturing polyacrylamide gels, and performing DNA sequence analyses on the extended products. Four categories of extension products, indicative of four different classes of late 19S RNA, were detected. One class was colinear with SV40 DNA at its 5' terminus, while three classes contained splices that fused residue 476 at the 5'-terminus of the body of this RNA to residues 444, 291, and 212, respectively. The most abundant 19S species contained the splice from residues 291-476. The extension products terminated at a number of different sites. Multiple species stopped at residues 182 and 243 with the sequence T-A-A. These sites probably represent the 5'-termini of in vivo species of 19S RNA's, and the available evidence suggests that extended products stopping at other sites with the sequences T-A(A) and T-A, as well as certain other sequences, may also arise from discrete in vivo RNA's. For each of the three different gaps found in the late 19S RNA's, as well as for four additional gaps analyzed in the late 16S and early 19S RNA's of SV40, identical di-, tri-, or tetranucleotide sequences lay on the un-gapped precursor at sites that underwent splicing. These sequences may be involved in determining the specificity of the splicing reaction. (80 refs)

79-1626 Interference in SV40 DNA Infections: A Possible Basis for Cellular Competence. (Eng) Wilson, J. H. (Marrs McLean Dept. Biochemistry, Baylor Coll. Medicine, Houston, TX, 77030). *Virology* 91(2): 380-388; 1978.

The ability of other DNAs to interfere with infection by wild-type simian virus 40 (SV40) DNA was studied. Temperature sensitive (ts) SV40 DNA interfered with plaque formation by nondefective tester DNA in the first cycle of infection. Apparently, the interference phenomenon primarily limited the number of cells in which a normal infection was initiated.

Linear ts SV40 DNA's interfered about 5- to 10-fold less efficiently than the corresponding closed-circular DNA's, and structurally similar closed-circular DNA's (SV40, PM2 and X174) varied over a 100-fold range in their ability to interfere. The difference in interference by structurally similar DNA's suggests that interference may be influenced by nucleotide sequence. Plaque formation by tester DNA was interfered with when its infection was preceded by infection with interfering DNA, but when infection by tester DNA preceded infection by interfering DNA, interference was not observed. The results suggest that: interference occurs early in infection and is independent of any viral gene product; interference occurs after the DNA's interact with the cell; interference depends in part on nucleotide sequence information, suggesting that the site of interference may be intracellular, perhaps nuclear; and interference could be the basis for the limited response of African green monkey kidney cells to SV40 DNA that has previously been attributed to cellular "competence." (17 refs)

- 79-1627 SV40-transformed Human Diploid Cells That Remain Transformed Throughout Their Limited Lifespan.** (Eng) Gotoh, S. (Dept. Microbiology and Immunology, Div. Biology and Biomedical Sciences, Washington Univ. Sch. Medicine, St. Louis, MO, 63110); Gelb, L.; Schlessinger, D. *J Gen Virol* 42(2): 409-414; 1979.

WI-38 human diploid fibroblasts (FB's) were infected with simian virus 40 (SV40), apparently transformed foci were identified and subcultured, and the foci were observed as they approached crisis to determine why SV40 infection of FB cultures induces the survival of rare cells that can grow into permanent cell lines. Three to 6 wk after infection, 91 well-separated foci were identified; however, only 46 grew sufficiently to be expanded to a confluent culture in a 60-mm petri dish. The fastest-growing (earliest-appearing) foci were subcultured most successfully. None of the foci were able to grow in soft agar. Twenty-four foci grew only through passage 41; the remaining 22 foci survived to a max of 64-65 passages. During the entire growth period, including crisis, the cells of each subculture showed the morphology and SV40 tumor-antigen positivity of transformed cells, which indicates that SV40 transformation per se is insufficient to confer indefinite growth on human diploid FB's. These results are consistent with the commitment theory of FB senescence, which suggests that FB tend to lose their capacity for indefinite growth by an irreversible change (commitment) that occurs many generations before cell division ceases. However, this theory does not explain how SV40 transformation promotes the survival of any cells from mass culture. Either uncommitted cells can exist in cultures in crisis but cannot overgrow the mass of undividing cells or SV40 transformation can reverse the terminal cessation of cell division in rare cells. If reversal of commitment is required to promote survival, a special transformation event must also be postulated or survivors would be more common. The only hint of a possible physiological correlate of this event noted was the inability of the 91 subcultures to grow in soft agar. (21 refs)

- 79-1628 Karyotype Evolution of the Simian Virus 40-transformed Human Cell Line LNSV.** (Eng) Begovich, A. (Dept. Pediatrics, Univ. California, San Diego Sch. Medicine, La Jolla, CA); Francke, U. *Cytogenet Cell Genet* 23(1/2): 3-11; 1979.

Trypsin-Wright's banding was used to analyze the chromosomes of two sublines of the simian virus 40-transformed Lesch-Nyhan cell line LNSV, which was derived from the fibroblasts of a patient with hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency. The chromosome number per cell in the subline GM-847 ranged from 64 to 90 with a mean of 77; that in subline LNSV ranged from 62 to 81 with a mean of 75. Some chromosomes were present at about the same frequency in both sublines, whereas others, especially 2, 7, 11, and 18, were much more common in GM-847. Nineteen rearranged chromosomes that were observed in at least 40% of metaphases were set aside as marker chromosomes, and their probable derivation from normal chromosomes was described according to Paris Conference (1971) nomenclature. Most markers were the result of apparent terminal deletions, although some resulted from translocations, interstitial deletions, or duplications. In addition to these markers, each cell possessed a number of unique rearrangements. Heterogeneity within the two sublines appeared to increase with time in culture, and no evidence was found for evolution of a karyotypically stable cell population. (23 refs)

- 79-1629 Photodynamic Induction of an Oncogenic Virus In Vitro.** (Eng) Bockstahler, L. E. (Health, Food and Drug Admin., Rockville, MD, 20857); Cantwell, J. M. *Biophys J* 25(1): 209-213; 1979.

A study was carried out with simian virus 40 (SV40)-transformed hamster kidney cells to determine whether photodynamic induction of virus can occur with a mammalian virus-host system. Cell cultures were treated with different concentrations of proflavine (0-12 μ M), exposed to visible light for 1 hr (10^3 J/m²), and incubated for virus expression. For the range of dye concentrations examined, induction of SV40 was observed between 0.5 and 3 μ M. The optimum level of SV40 induced (1 μ M proflavine) represented an increase in virus production of three orders of magnitude above the spontaneous background level. No virus induction above background levels was found by treatment of cells with either proflavine or light alone. These results demonstrate that photodynamic induction of virus can occur with a mammalian virus-host cell system. (11 refs)

- 79-1630 Binding and Transcription of Native and Chemically Modified SV40 DNA by *Escherichia coli* DNA-dependent RNA Polymerase.** (Eng) Hale, P. L. (Birmingham Medical Center, Univ. Alabama, Birmingham, AL). *Diss Abstr Int B* 39(8): 3697; 1979. (no refs)

- 79-1631 Structural Relationship Between the 100,000- and 17,000-Molecular-Weight T Antigens of Simian Virus 40 (SV40) as Deduced by Comparison with the SV40-specific Proteins Coded by the Nondefective Adenovirus Type 2-SV40 Hybrid Viruses.** (Eng) Linke, H. K. (Molecular Biology Inst., Univ. California, Los Angeles, CA, 90024); Hunter, T.; Walter, G. *J Virol* 29(1): 390-394; 1979.

The two-dimensional peptide maps of the methionine-containing tryptic peptides of the 100,000-dalton (100K) and 17K tumor (T) antigens of simian virus 40 (SV40) were compared. The 100K and 17K T antigens shared a common N-terminal region coded between the initiator AUG triplet at 0.65 map units and 0.59 map units, whereas none of the sequences in the 17K antigens arose from the region between 0.54 and 0.17 map units. The 17K T antigen had 2 peptides not found in the 100K T antigen and the 100K T antigen had 14 unique peptides. The unique sequences of the 17K T antigen probably originate between 0.59 and 0.54 map units. An almost complete identity existed between the peptides of 100K T antigen and those of the 95K protein of cells infected by a nondefective adenovirus type 2-SV40 hybrid virus. This, coupled with the demonstrated absence of peptides R and S in the 95K protein, suggests that the messenger RNA (mRNA) for the 95K protein is lacking the sequences between 0.59 and 0.54 map units and has undergone the same splicing event as the smaller of the two early SV40 mRNA's, which codes for the 100K T antigen. These data support a proposed model for the expression of the early region of SV40. (22 refs)

- 79-1632 Serological Evidence for Antigenic Differences Between the Mason-Pfizer Monkey Virus (MPMV) and an MPMV-like Virus (PMFV) Detected in a Malignant Permanent Human Cell Line.** (Eng) Micheel, B. (Central Inst. Cancer Res., Academy Sciences of the GDR, Lindenberger-Weg 70/80, DDR-1115 Berlin-Buch, E. Germany); Baumbach, L.; Wunderlich, V.; Niezabitowski, A.; Bierwolf, D. *Eur J Cancer* 15(1): 101-108; 1979.

Mason-Pfizer monkey virus (MPMV) and an MPMV-like virus (PMFV) detected in a malignant continuous human cell line were compared in immunofluorescence tests. Anti-MPMV and anti-PMFV sera reacted specifically with the cytoplasm of both MPMV- and PMFV-infected but not with uninfected cells. Immunofluorescence absorption showed that, in addition to the common specificities, both viruses have distinct antigens. It was not possible, under the conditions of this experiment, to determine on which polypeptide these antigenic determinants are localized. It is concluded that MPMV and PMFV must be regarded as different types of a closely related virus group. (23 refs)

- 79-1633 Sarcoma Virus-specific Phosphoproteins are Packaged in "Rescued" Type C Virions.** (Eng) Sen, A. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD, 20014); Halverson, D. O.; Rapp, U. R.; Todaro, G. J.

Virology 92(1): 245-251; 1979.

Phosphorylated proteins in sarcoma virus pseudotypes obtained by acute infection of nonproductively transformed cell lines with a variety of helper viruses were analyzed by denaturing gel filtration. Each sarcoma virus appeared to specify at least one major structural phosphoprotein that was present in the pseudotype virions but not in the helper virions. The major phosphoprotein specific for particular sarcoma virus pseudotypes appeared to be independent of the cell lines. However, the amount of the new phosphoprotein relative to the helper structural phosphoprotein varied with the helper used as well as with the time elapsed between the establishment of an acute infection with helper virus and the analysis of phosphoprotein in the pseudotypes. Nuclease treatment did not alter the av mol wt or the size heterogeneity of the sarcoma virus-specific phosphoprotein molecules, which suggested that they are not covalently conjugated nucleoprotein complexes. These sarcoma viral phosphoproteins or related products may be involved in the maintenance of transformation in culture and/or tumor immunity in virus-exposed animals. (29 refs)

- 79-1634 Studies of Simian Sarcoma and Simian Sarcoma-associated Virus: I. Analysis of Viral Structural Proteins, and Preparation and Characterization of Antiserum Specific for Viral Envelope Components.** (Eng) Deinhardt, F. (Pettenkofer Institut, Pettenkoferstrasse 9a, D-8000 Munich 2, W. Germany); Bergholz, C.; Hunsmann, G.; Schneider, J.; Thiel, H. J.; Beug, H.; Schafer, W. *Z Naturforsch C* 33(11/12): 969-980; 1978.

The structural proteins of simian sarcoma virus (SSV) and simian sarcoma-associated virus (SSAV) were analyzed by gel electrophoresis, and a virus-specific antiserum that appears to react predominantly with viral envelope components was prepared and characterized. The protein pattern of SSV was very similar to that of murine leukemia virus (MuLV). The major polypeptides identified were glycoproteins of 69,000 and 71,000 daltons (gp69/71), envelope proteins p15(E) and p12(E), and internal proteins p31, p15, p12, and p10. As in MuLV, p12 stained reddish with Coomassie blue, but a p15 core protein [p15(C)] analogous to the p15(C) of MuLV and distinct from p15(E) was not clearly identified. Using antisera specific for individual components of Friend leukemia virus (FLV), cross-reactions were observed between proteins p15(E), p12(E), and p31 of SSV and FLV and, to a minor degree, between their respective major glycoproteins. An antiserum reacting strongly, specifically, and almost exclusively with SSV gp69/71, p15(E) and p12(E) was prepared by inoculating a goat with its own cells that had been transformed in vitro with SSV and grown in goat serum. Comparative studies with this antiserum in complement-fixation and Ouchterlony tests confirmed the reported strong antigenic similarities between SSV and gibbon ape lymphoma virus but did not identify any interspecies reactivity. This lack of interspecies reactivity may impair the value of the goat an-

tiserum for identifying and evaluating new viral isolates or viral components from human material. (82 refs)

- 79-1635 Antibody Responses to Herpesvirus Papio Antigens in Baboons with Lymphoma.** (Eng) Neubauer, R. H. (Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21501); Rabin, H.; Strnad, B. C.; Lapin, B. A.; Yakovleva, L. A.; Indzie, E. *Int J Cancer* 23(2): 186-192; 1979.

An Epstein-Barr virus-related herpesvirus, termed herpesvirus papio (HVP), was isolated from baboons (*Papio hamadryas*) at the Institute of Experimental Pathology and Therapy, Sukhumi, USSR, where there is a continuing outbreak of lymphoma. Sera from diseased baboons and from age- and sex-matched control animals were examined for antibodies to HVP antigens. Animals with lymphoid disease had antibodies to HVP virus capsid, early, soluble, and nuclear antigens at higher frequencies and at higher titers than did control animals. Antibody titers were not age- or sex-related. No concordancy was detected for antibodies to soluble and nuclear antigens. Examination of the sera for antibodies to two other widely distributed viruses of hamadryas baboons, cytomegalovirus and foamy virus, did not indicate a disease-related role for either of these viruses. (29 refs)

- 79-1636 Expression of Fc Receptors, Ia Antigens, and B2 Microglobulin after In Vitro Herpes Simplex Virus Infection of Human Lymphoid Cells (Meeting Abstract).** (Eng) Dorval, G. (Royal Victoria Hosp., Montreal, Canada H3A 1A1); Bourkas, A. F.; Menezes, J. *Fed Proc* 38(3, part 2): 927; 1979. (no refs)

- 79-1637 Polyamine Turnover and Leakage During Infection of HeLa and L-Cells with Herpes Simplex Virus Type 1.** (Eng) McCormick, F. (Translation Lab., Imperial Cancer Res. Fund, London WC2, England). *Virology* 91(2): 496-503; 1978.

Polyamine turnover was studied in HeLa and L cells during infection with herpes simplex virus type 1 (HSV-1). Little spermine was lost from uninfected L or HeLa cells; spermidine was lost more rapidly, presumably due to conversion to spermine. Infection of L cells with HSV-1 resulted in almost complete loss of spermidine and spermine within 20 hr, whereas HeLa cells lost only 18% and 26% of their spermidine and spermine, respectively, during infection. In uninfected HeLa and L cells, the specific activity of spermine decreased with a half-life of 22 and 25 hr, respectively. In infected cells, the specific activity of spermine remained constant, suggesting that spermine is not synthesized after infection. Changes in the specific activity of spermidine followed those of spermine. L cells became extremely permeable to polyamines early in infection, whereas HeLa cells did not. The addition of spermidine or spermine had little effect on the production of infectious virus, which was 20-fold greater in HeLa than in L cells. The data indicate that the cell

polyamine pools do not limit the production of infectious virus. (21 refs)

- 79-1638 Concanavalin A-mediated Agglutination of 3T3 Cells after Exposure to UV-irradiated Herpes Simplex Virus.** (Eng) Taguchi, F. (Dept. Microbiology, Kitasato Univ. Sch. Hygienic Sciences, Sagamihara-shi, Kanagawaken 228, Japan); Hara, K.; Nagaki, D. *Microbiol Immunol* 22(10): 597-608; 1978.

The effect of UV-irradiation of herpes simplex virus type 2 (HSV-2) on concanavalin A (Con A)-mediated agglutination (agg) of infected Swiss 3T3 cells was studied. HSV-2 was irradiated for 1-20 min before being injected into cultures at a multiplicity of infection of 2 plaque-forming units/cell. Virus was adsorbed for 90 min before the infected cells were examined for Con A agglutinability. Three different phases of agg were observed. The agglutinability began to increase at 3, 4, or 72 hr postinfection (pi). Early 1 agg, detected at 3 hr pi, was induced by treating cells with HSV-2 that was either active or irradiated <5 min, and it was inhibited by actinomycin D (1 µg/ml) or cycloheximide (50 µg/ml). Early 2 agg began to increase at 4 hr pi when cells were inoculated with HSV-2 irradiated for 7-20 min, and it was not affected by either inhibitor. HSV-2 irradiated for 6 min failed to induce either type of agglutinability. Late agg, observed 72 hr pi, was detected in cultures that had been treated with HSV-2 irradiated for 4-15 min. Virus irradiated for 6-8 min was most efficient at inducing late agg. HSV-2-transformed cells were agglutinated without exception by low concentrations of Con A. In addition, a high transformation rate was observed 3-4 wk pi in cell cultures exposed to HSV that had been irradiated for 6-8 min. These results indicate that the optimal duration of UV-irradiation of HSV-2 seems to be limited to 6-8 min for two different phenomena. (21 refs)

- 79-1639 Effect of Actinomycin D on the Expression of Herpes Simplex Virus-Common Surface Antigen in Cells Transformed by Herpes Simplex Virus Type 2.** (Eng) Kimura, S. (Dept. Bacteriology, Sch. Medicine, Tokushima Univ., Tokushima 770, Japan); Okazaki, K.; Yoshida, N.; Ohnishi, Y. *J Virol* 29(1): 161-169; 1979.

Using rabbit antiserum hyperimmune to herpes simplex virus type 1 (HSV-1), the expression of HSV common surface antigen(s) (CSA) was studied by indirect immunofluorescence using hamster cells transformed by HSV type 2 (155-4 cells) and derived tumor cells (155-4T). The effect of actinomycin D (A-D) treatment of the cells on CSA expression was also studied. Antiserum to HSV-1 reacted specifically with CSA on the plasma membranes of 155-4 and 155-4T cells. A peak of CSA-positive 155-4 cells was observed 3-5 hr after seeding, but no such peak was observed with 155-4T cells. The initial increase in CSA-positive 155-4 cells after seeding was maintained for 20 hr by treatment with A-D, the effect lasting for several hours after removal of the drug and being greatest with a drug concentration of 2 µg/ml. Treatment with A-D

did not affect CSA expression in 155-4T cells. The A-D effect of 155-4 cells was partially inhibited by 10-20 $\mu\text{g}/\text{ml}$ of puromycin and completely inhibited by 50 $\mu\text{g}/\text{ml}$, indicating that new protein synthesis was required for A-D-enhanced CSA expression. The protease inhibitor antipain (0.5 mM) did not affect growth or CSA expression of 155-4 cells, but it abrogated the enhancing effect of A-D. The data indicate that two kinds of CSA expression occur in transformed 155-4 cells: one type is expressed soon after seeding, does not require further protein synthesis, and is insensitive to antipain; the other is expressed in response to A-D, requires protein synthesis, and is sensitive to antipain. (32 refs)

79-1640 Herpes Simplex Virus Type 2 Functions Expressed During Stimulation of Human Cell DNA Synthesis. (Eng) Kucera, L. S. (Dept. Microbiology and Immunology, Bowman Gray Sch. Medicine, Wake Forest Univ., Winston-Salem, NC, 27103); Edwards, I. *J Virol* 29(1): 83-90; 1979.

To identify herpes simplex virus type 2 (HSV-2)-specific functions expressed during stimulation of human embryo fibroblast (HEF) DNA synthesis, cultures were partially arrested during DNA synthesis by pretreatment with 5-fluorouracil and maintained in 0.2% serum medium during virus infection. De novo RNA and protein syntheses were continuously required during HSV-2 stimulation of HEF DNA replication. During this stimulation, the virus markedly increased the rate of thymidine transport and intracellular thymidine metabolism. In addition, HSV-2-specific thymidine kinase (TK) activity was expressed. HSV-2 stimulation of HEF DNA synthesis represented predominantly semiconservative replication and some cell DNA repair. Thus, HSV-2 stimulation of cellular DNA synthesis involved at least four virus-specific functions: induction of thymidine transport, HSV-2 TK activity, semiconservative replication, and repair of cellular DNA. The ability of HSV-2 to stimulate human cell DNA synthesis suggests that the virus is capable of influencing the normal regulatory processes of resting cells. (21 refs)

79-1641 Characterization of Cross-reacting Antigens on the Epstein-Barr Virus Envelope and Plasma Membranes of Producer Cells. (Eng) Thorley-Lawson, D. A. (Sidney Farber Cancer Inst., Harvard Medical Sch., 44 Binney St., Boston, MA, 02115). *Cell* 16(1): 33-42; 1979.

A study was undertaken to design and implement a technique for characterizing and purifying the membrane antigen/neutralizing antigen complex of Epstein-Barr virus (EBV). A rabbit antiserum was prepared against the B95-8 transforming strain of EBV. The antiserum has a high virus-neutralizing titer (approx 1:1,000) against both marmoset B95-8 EBV and human P3HR-1 EBV. The neutralizing antibodies were absorbed completely with EBV producer cell lines, but not with nonproducer cell lines or producer cell lines treated with phosphonoacetic acid (PAA), which blocks expression of late

viral antigens. After repeated absorption with PAA-treated B95-8, the serum remained reactive with the membranes of producer cell lines, as determined by immunofluorescence or the ^{125}I -Staphylococcal protein A radioimmunoassay. Thus, neutralizing antigens are expressed on the membranes of producer cell lines. The polypeptides recognized by the antiserum were characterized by immunoprecipitation studies as having mol-wts of approx 150,000 and 75,000. Since the antiserum was raised against virions, these two polypeptides are probably virion structural proteins or their precursors, and at least one of them is probably part of the membrane antigen complex. (31 refs)

79-1642 Differences in EBV Receptor Concentration Between In Vitro EBV-converted Lymphoma Sublines Reflect Biological Differences Between the Converting Viral Substrains. (Eng) Klein, G. (Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm 60, Sweden); Manneborg, A.; Steinitz, M. *Int J Cancer* 23(2): 197-200; 1979.

The Epstein-Barr virus (EBV)-receptor concentration of two EBV-negative human B-cell lymphoma lines (BJAB and Ramos) was determined before and after in vitro conversion with the transforming B95-8 (B) or the cytopathic P3HR-1 (P) EBV substrains into permanent EBV-carrying sublines. Receptors were measured by a quantitative EBV-absorption bioassay. The absorption index of two B-virus-converted BJAB sublines was not significantly different from that of BJAB. In contrast, a P-virus-converted line showed significantly reduced EBV-absorbing capacity. The results were similar for Ramos and its converted sublines. Thus, the EBV-receptor concentration of all P-virus-converted sublines was significantly reduced compared with that of the B-virus-converted sublines. P-virus conversion of Ramos and BJAB has probably selected cells with a low but clearly positive EBV-receptor expression. Conceivably, cells with few receptors might be hit by a transforming particle without the major risk of also capturing a cytopathic particle, whereas cells with a high EBV-receptor concentration are more likely to capture both. (20 refs)

79-1643 Epstein-Barr Virus-Specific RNA. III. Mapping of DNA Encoding Viral RNA in Restraining Infection. (Eng) Powell, A. L. (Dept. Medicine, Univ. Chicago, Chicago, IL, 60637); King, W.; Kieff, E. *J Virol* 29(1): 261-274; 1979.

The location within the map of the Epstein-Barr virus (EBV) genome of the DNA that encodes the viral RNA in the polyadenylated [poly(A)+] and nonpolyadenylated [poly(A)-] RNA fractions of Namalwa cells (originally obtained from a Burkitt tumor) was studied. Hybridization of ^{32}P -labeled EBV DNA homologous to Namalwa poly(A)+ or poly(A)- RNA with restriction endonuclease fragments of EBV (B95-8) DNA indicated that these RNA's are encoded by DNA contained primarily in the *Hsu* I A/*Eco*RI A and

Hsu I B/*Eco*RI A fragments and, to a lesser extent, by DNA in other fragments of the EBV genome. Hybridizations of Namalwa poly(A)+ and poly(A)- RNA in soln to denatured labeled *Eco*RI A or B fragments, *Hsu* I A, B, or D fragments, and *Hsu* I A *Eco*RI A or *Bam* I S fragments and of Raji polyribosomal poly(A)+ RNA to the *Eco*RI A fragment indicated that Namalwa poly(A)+ RNA is encoded primarily by 6×10^5 daltons of a 2×10^6 -dalton segment of DNA, *Bam* I S, which is tandemly reiterated (approx 10 times) in the *Hsu* I A/*Eco*RI A fragment and is encoded to a lesser extent by DNA in the *Hsu* I B, *Eco*RI B, and *Hsu* I D fragments. Raji polyribosomal poly(A)+ RNA is encoded by a fraction of the *Eco*RI A fragment similar to the one that encodes Namalwa poly(A)+ RNA. The fraction of the *Bam* I S fragment homologous to Namalwa poly(A)- RNA is similar to the fraction homologous to Namalwa(A)+ RNA. However, Namalwa poly(A)- RNA is homologous to a larger fraction of the DNA in the *Hsu* I B, *Hsu* I D, and *Eco*RI B fragments. (56 refs)

79-1644 **Complementation of Infecting Epstein-Barr Virus by Intrinsic Viral Genomes in Human Lymphoblastoid Cells (Meeting Abstract).** (Eng) Lidin, B. (Dept. Microbiology, Univ. Alabama in Birmingham, Birmingham, AL, 35294); Lamon, E. W.; Alford, C. A. *Fed Proc* 38(3, part 2): 1071; 1979. (no refs)

79-1645 **Antibody-Effects on the Expression of Membrane Antigens Specified by Epstein-Barr Virus (Meeting Abstract).** (Eng) Liang, W. (La Rabida-Univ. Chicago Inst., Chicago, IL, 60649); Cohen, E. P. *Fed Proc* 38(3, part 2): 1177; 1979. (no refs)

79-1646 **Epstein-Barr Virus-induced Oncogenesis in Immunodeficient Patients (Meeting Abstract).** (Eng) Purtilo, D. (Dept. Pathology, Univ. Massachusetts Medical Center, Worcester, MA, 01505); Hamilton, J.; Sullivan, J.; Paquin, L.; Bhawan, J.; Sakamoto, K. *Lab Invest* 40(2): 296; 1979. (no refs)

79-1647 **Nonconditional Replication Mutants of Type C and Type D Retroviruses Defective in *gag* Gene-coded Polypeptide Post-translational Processing.** (Eng) Sacks, T. L. (Viral Genetics Section, Lab. Cellular and Molecular Biology, NCI, Bethesda, MD, 20014); Devare, S. G.; Blennerhassett, G. T.; Stephenson, J. R. *Virology* 91(2): 352-363; 1978.

The rapid isolation and preliminary characterization of nonconditional replication-defective mutants of C-type retroviruses of primate and nonprimate origin and a representative D-type retrovirus are described. By this means, 6 RD114, 3 M7 baboon, 4 Rauscher murine leukemia virus (R-MuLV), and 9 squirrel monkey retrovirus (SMRV) mutant clones were isolated. Although defective for virus production, all but

two of the mutant clones isolated were characterized by relatively high levels of *gag* and *env* gene-coded protein expression. Although expression of *gag* and *env* gene translational products was coordinate in most of the R-MuLV and SMRV mutant clones, certain clones nonproductively infected with either RD114 or M7 baboon virus showed noncoordinate synthesis. Further analysis of representative mutant clones indicated impaired *gag* gene-coded polypeptide posttranslational processing. This latter observation made possible identification of the component structural proteins of both RD114 and SMRV *gag* gene-coded precursor polypeptides. The susceptibility of many of the clones to superinfection by wild-type virus indicated that the defect in virus production was due to mutation in the viral, rather than host, genome. Several nonproductively infected clones, on the other hand, were resistant to superinfection. The demonstration of greater cross-interference to superinfection between M7, RD114, and SMRV than between any of these viruses and the amphotropic murine C-type virus isolate 4070-A corroborates the presence of shared envelope glycoprotein determinants between primate-derived C- and D-type viruses. (28 refs.)

79-1648 **Enhanced Induction of Growth of B Lymphoblasts from Fresh Human Blood by Primate Type-C Retroviruses (Gibbon Ape Leukemia Virus and Simian Sarcoma Virus).** (Eng) Markham, P. D. (Litton Bionetics, Inc., 7300 Pearl St., Bethesda, MD, 20014); Ruscetti, F.; Salahuddin, S. Z.; Gallagher, R. E.; Gallo, R. C. *Int J Cancer* 23(2): 148-156; 1979.

A systematic study was made of the infection of fresh human hematopoietic cells by primate C-type retroviruses. Continuously growing B-lymphoblast cell lines were established from the peripheral blood of 11/21 Epstein-Barr virus (EBV)-seropositive human donors after exposure to viruses of the gibbon ape leukemia virus (GALV)-simian sarcoma virus/simian sarcoma-associated virus (SiSV/SiSAV) group. The incidence of growth induction upon exposure to baboon endogenous virus (BaEV), feline leukemia virus (FeLV), or to uninfected monolayer cultures was < 10%. WBC from the peripheral blood of leukemic patients gave similar results, but exposure of fresh peripheral blood from eight normal EBV-seronegative donors to the same viruses did not result in induction of cell growth. The established cell lines were polyclonal B lymphoblasts, as determined by morphological, cytochemical, immunological, and functional properties. The cells expressed EBV nuclear antigen (EBNA test), formed rosettes with complement-activated sheep or bovine erythrocytes (EAC-rosette test), but not with untreated erythrocytes (E-rosette test), and were positive for one or more surface-bound immunoglobulins. They were also karyotypically normal, as determined by standard chromosome analysis and by trypsin-Giemsa banding techniques. However, unlike other reported newly established diploid B-lymphoblast cell lines, cells from approx 80% of the cultures tested grew as locally invasive tumors when inoculated into 1- to 3-wk-old athymic nude mice and formed colonies in semisol-

id medium. Lymphoblasts from nude mouse tumors were readily reestablished as suspension cultures that retained their lymphoblastic properties and remained karyotypically normal. These studies indicate that under certain conditions, C-type retroviruses of the GALV-SiSV/SiSAV group directly or indirectly increase the incidence of transformation of human B lymphocytes. (57 refs)

79-1649 Biology and Virology of the Human Malignant Lymphomas. 1st Milford D. Schulz Lecture. (Eng) Kaplan, H. S. (Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305); Goodenow, R. S.; Gartner, S.; Bieber, M. *Cancer* 43(1): 1-24; 1979.

Permanent cell lines were established from 12 diffuse histiocytic lymphomas (SU-DHL-1 to -12), 3 American Burkitt's lymphomas (SU-AmB-1 to -3), 2 acute lymphoblastic leukemias (SU-ALL-1 and -2), and 3 diffuse undifferentiated lymphomas (SU-DUL-1 to -3). The cultured cells displayed neoplastic characteristics, as manifested by heterotransplantability in congenitally athymic nude mice and by cytogenetic abnormalities in early passage generations. The three AmB and several of the DHL and DUL lines were of B-lymphocytic origin, whereas the two ALL lines were of T-lymphocytic origin. SU-DHL-1 and -2 appeared to be of true histiocytic origin; two others exhibited no markers and were designated "null" cells. All 10 DHL lines studied to date, as well as SU-DUL-1, were devoid of Epstein-Barr virus (EBV) genomes by the EB nuclear antigen test, whereas 2/3 AmB lines were positive. Spontaneous production of a C-type RNA virus was first detected in the postmitochondrial cytoplasmic fractions and culture fluids of SU-DHL-1. Screening assays for the detection of reverse transcriptase (RT)-positive particles in the culture fluids of the other cell lines indicate that 8/15 cell lines tested spontaneously initiated C-type RNA virus production. After partial purification by ion-exchange and affinity chromatography, the RT of the virus isolated from SU-DHL-1 cells is partially inhibited by antibodies to the RT's of C-type viruses of subhuman primate and endogenous feline, but not of murine, origin. Conversely, antibody prepared against the purified SU-DHL-1 viral RT, at concentrations that maximally inhibit the homologous enzyme, partially inhibits the RT's of subhuman primate C-type viruses, but has little or no inhibitory activity against the RT's of feline or murine leukemia viruses. The viruses produced by SU-DHL-1 and SU-AmB-3 are infectious for normal human peripheral blood mononuclear cells, normal human bone marrow cells, and certain human lymphoblastoid cell lines. After infection by these viruses, the mononuclear and bone marrow cells exhibit striking changes in growth behavior and morphology that, although not permanently sustained, have many of the features of abortive transformation. (57 refs)

79-1650 Hepatocellular Carcinoma in the USA, Etiologic Considerations. Localization of Hepatitis B Antigens. (Eng) Omata, M. (Sch. Medicine, Univ. Southern

California, Los Angeles, CA); Ashcava, M.; Liew, C. T.; Peters, R. L. *Gastroenterology* 76(2): 279-287; 1979.

The serologic and tissue markers of hepatitis B virus (HBV) were studied in 50 patients in whom hepatocellular carcinoma (HCC) was confirmed at autopsy. Fifteen of 20 patients with nonalcoholic chronic liver disease and HCC showed at least one marker of HBV infection including serum hepatitis B surface antigen (HBsAg) in 11 patients and tissue hepatitis B core antigen (HBcAg) in 10. Of 22 patients with alcoholic cirrhosis and HCC, 2 showed evidence of HBV infection. The incidence of HBV markers among 63 alcoholic cirrhotic patients without HCC was 7.9%. One of eight patients with HCC and otherwise normal livers had HBsAg and serum antibody to HBcAg; this patient was a former drug user. Of 321 patients in another autopsy series who had died with moderate to advanced alcoholic cirrhosis, 22 had HCC. Of 39 patients who had died with B-viral chronic liver disease, 15 had HCC. The data indicate that there is a high incidence of HBV among HCC patients with nonalcoholic chronic liver disease in the US. If chronic active hepatitis type B were as common in the US as it is in Africa and Asia, the incidence of HCC might also be as high. (37 refs)

79-1651 Hepatocellular Carcinoma in a Hepatitis B Surface Antigen Carrier and Treatment with Adriamycin. (Eng) Fung, W. P. (Univ. Dept. Medicine, Royal Perth Hosp., Box X2213 GPO, Perth 6001, Western Australia, Australia); Surveyor, I.; Scott, G. R.; Laden, A. M. *Am J Gastroenterol* 70(4): 397-400; 1978.

A hepatocellular carcinoma (HCC) occurred in a 32-yr-old Caucasian male carrier of hepatitis B surface antigen (HBsAg). The patient was also positive for α -fetoprotein, but he was negative for hepatitis B surface antibody. Adriamycin (60 mg iv) was given four times at intervals of 3-6 wk. HBsAg and α -fetoprotein remained positive, and there was no significant change in tumor size or significant clinical improvement. The patient died 7 mo after confirmation of HCC. Postmortem examination showed numerous nodules of HCC with multiple foci of necrosis; the liver was fibrotic and cirrhotic. HBsAg has frequently been reported in patients with HCC, and familial clustering of HCC and HBsAg has been found. The present case further supports the hypothesis that hepatitis B virus may be involved in the cause of HCC. (17 refs)

79-1652 Hepatitis B Virus Antigens in Primary Hepatic Carcinoma: Immunofluorescent Techniques on Fixed Liver Tissue. (Eng) Trevisan, A. (Istituto di Medicina Clinica, Cattedra di Patologia Medica dell'Universita di Padova, Padova, Italy); Realdi, G.; Losi, C.; Ninfo, V.; Rugge, M.; Rampinelli, L. *J Clin Pathol* 31(12): 1133-1139; 1978.

Immunofluorescence techniques were used to determine the presence of hepatitis B surface antigen (HBsAg) and core antigen (HBcAg) in liver specimens obtained at necropsy

from 107 patients (77 men, 30 women aged 1-93 yr) with primary hepatocellular carcinoma (HCC). HBsAg was detected in the nonneoplastic liver tissue of 16 patients: 13 with Grade I, 2 with Grade II, and 1 with Grade III HCC. Cirrhosis was present in 11/16 patients, and the remaining 5 showed underlying chronic active hepatitis (3) or nonspecific reactive hepatitis (2). HBsAg-positive cells were scattered among the patients with cirrhosis or chronic active hepatitis, but a sheet distribution was found in the latter. HBsAg was also present in the cytoplasm of the cancer cells in eight patients (all Grade I). The number of HBsAg-containing cells was lower in the neoplastic tissue than in normal tissue. HBcAg in a granular pattern was detected in the nuclei of nonneoplastic cells in eight patients (6 Grade I, 1 Grade II, 1 Grade III); in six of these patients, HBcAg was also found in scattered nuclei in the neoplastic cells. In two other patients, which were negative for HBcAg but positive for HBsAg in nonneoplastic tissue, many cancer cells showed a positive nuclear reaction with anti-HBc serum. The nuclear pattern of HBcAg in neoplastic tissue was similar to that observed in the normal cells. Thus, hepatitis B virus (HBV) markers were detected mainly in the liver of patients with a well-differentiated tumor, and in all of these cases HBsAg and/or HBcAg were found also in the malignant cells. Although the tumor cells could have been infected after malignant transformation, a direct oncogenic role of HBV cannot be excluded. (21 refs)

- 79-1653 Sequence Analysis of Adenovirus DNA. I. Nucleotide Sequence at the Carboxy-terminal End of the Gene for Adenovirus Type 2 Hexon.** (Eng) Akusjarvi, G. (Dept. Microbiology, Univ. Uppsala, Biomedical Center, Box 581, S-751 23 Uppsala, Sweden); Pettersson, U. *Virology* 91(2): 477-480; 1978.

Adenovirus type 2 (Ad2) DNA was cleaved with restriction endonucleases *Bam*HI and *Bgl*II, and the nucleotide sequence of a 210-base pair fragment located between map positions 59.0 and 60.2 was determined. The sequence included a terminator, UAA, located within an AT-rich region 136-138 nucleotides to the right of the *Bam*HI cleavage site at position 59.0. A nearly perfect inverted repeat of this region occurred in a segment starting 22 nucleotides to the right of the *Bam*HI cleavage site. The codons immediately preceding the termination codon determined the sequence Thr-Pro-Phe-Ser-Ala-Gly-Asp-Ala-Thr-Thr. The established sequence thus included the codons for the 45 C-terminal amino acids of the Ad2 hexon and 75 nucleotides from the presumptive noncoding 3'-terminal part of the hexon messenger RNA. In the C-terminal part of the hexon gene, 75.6% of the coding triplets terminated with a C or, less commonly, a G; only 3/45 codons ended with an A. (9 refs)

- 79-1654 Mapping of the DNA Fragments Produced by Cleavage of *Eco*RI F Fragment of Adenovirus 2 with *Hae*III, *Hpa*II and *Alu*I.** (Eng) Herisse, J. (Laboratoire d'Hématologie Experimentale, Centre Hayem-Hopital Saint-Louis, 75475 Paris Cedex 10, France); Courtois, G.; Galibert, F. *Gene* 4(4): 279-294; 1978.

The physical map of the cleavage sites of several restriction endonucleases for the adenovirus 2 *Eco*RI F fragment was established. Hydrolysis of this fragment with *Hae*III, *Hpa*II, and *Alu*I gave 9, 11, and 11 fragments, respectively. Their size ranged from 20 base pairs for the smallest *Hpa*II K fragment to 585 base pairs for the largest *Alu*I A fragment. The order of the fragments was deduced mainly from partial hydrolysis analyses. The relative order of all restriction sites and the distance in nucleotides between them were obtained by secondary hydrolyses of each restriction fragment by the other two enzymes. The position of the *Kpn*I, *Hind*III, *Mbo*I, and *Sma*I sites within the *Eco*RI F fragment was also determined. (16 refs)

- 79-1655 Regulation of an Early RNA Transcribed from the Transforming Segment of the Adenovirus 2 Genome.** (Eng) Eggerding, F. (Dept. Pathology, Univ. California, Center Health Sciences, Los Angeles, CA, 90024); Raskas, H. J. *Virology* 91(2): 312-320; 1978.

Studies that suggest that the cytoplasmic concentration of the 22S messenger RNA (mRNA) is regulated by a second mechanism that supplements the coordinate regulation of the other major early mRNA's are presented. Early cytoplasmic RNA transcribed from the left end of the adenovirus 2 genome (region 1) is composed of two major size classes that migrate as 22S and 13S RNA's. Previous studies have shown that treatment with inhibitors of protein synthesis such as cycloheximide (CH) resulted in a significantly increased (10-fold) accumulation of all major size classes of cytoplasmic early RNA except a 22S species encoded by region 1. To clarify this differential effect of CH, the metabolism of region 1 RNA was compared in several experiments. The kinetics of accumulation of these RNA's in the absence of drug was analyzed beginning 3 hr after infection. The 13S size class accumulated more rapidly than the 22S RNA; after 2 hr of labeling, there was a threefold excess of 13S RNA compared with cultures labeled for 3 hr. Chase experiments using either actinomycin D in the absence of CH or cold uridine when CH was present demonstrated that the 22S RNA was more stable than the 13S size class. Thus, a 22S species is unlikely to serve as precursor to a major smaller RNA. Early RNA's synthesized in the presence of the amino acid analogs canavanine or β -hydroxynorvaline also contained increased amounts of region 1 13S RNA but not the 22S size class. To determine the effect of delayed CH addition, infections were performed in the absence of inhibitors and CH was then added 4 hr later. Under these conditions, the 22S RNA synthesized from 4.5 to 6.5 hr accumulated in increased amounts, comparable to the other early RNA's. The results suggest that a protein synthesized early in infection regulates the cytoplasmic concentration of 22S RNA. (33 refs)

- 79-1656 Splicing Patterns of Nuclear Precursors to the mRNA for Adenovirus 2 DNA Binding Protein.** (Eng) Goldenberg, C. J. (Dept. Pathology, Div. Biology, Bi-

omedical Sciences, Washington Univ. Sch. Medicine, St. Louis, MO, 63110); Raskas, H. J. *Cell* 16(1): 131-138; 1979.

The relationship of nuclear and cytoplasmic RNA's from early region 2 of the adenovirus 2 (Ad2) genome (map positions 61.6-75.0) was determined. Structural analysis demonstrated that nuclear 23S and 20S RNA's lack intervening sequences (map positions 74.6-68.8) that are also absent from the cytoplasmic messenger RNA (mRNA). The nuclear 28S RNA, however, has sequences complementary to the intervening DNA sequences. Analysis of colinear transcripts from the I strand of region 2 suggested that nuclear 28S and 23S RNA's contain the intervening sequences from a second splice (map positions 68.3-66.3). The nuclear 20S RNA and the mature cytoplasmic mRNA lack these sequences. Colinear polyadenylated transcripts were detected from the r strand of region 2; these transcripts have no apparent relationship to early mRNA. In continuous-labeling experiments, the 28S and 23S species reached a steady state within 30 min, whereas the amounts of nuclear and cytoplasmic 20S RNA's continued to increase for at least 3 hr. This labeling pattern suggests that the 28S and 23S species are precursors of the 20S RNA. A processing model for mRNA is proposed in which the intervening DNA sequences of the 72K DNA binding

protein gene are transcribed in its mRNA precursor (28S). These sequences are then removed sequentially to generate first a 23S intermediate and then a 20S nuclear RNA that will be transported to the cytoplasm as a mature mRNA. (48 refs)

See also:

*(Rev.): 79-1248, 79-1249, 79-1250, 79-1251, 79-1252, 79-1253, 79-1254, 79-1255, 79-1256, 79-1257, 79-1277, 79-1290.

*(Chem.): 79-1412, 79-1442, 79-1446.

*(Immun.): 79-1658, 79-1663, 79-1668, 79-1672, 79-1673, 79-1681, 79-1682, 79-1685, 79-1688, 79-1689.

*(Path.): 79-1693, 79-1702, 79-1703.

*(Epid.-Biom.): 79-1760, 79-1761, 79-1781.

- 79-1657 Tumor Metastases and Cell-mediated Immunity in a Model System in DBA/2 Mice. IV. Antigenic Differences Between a Metastasizing Variant and the Parental Tumor Line Revealed by Cytotoxic T Lymphocytes.** (Eng) Schirmacher, V. (Institut für Immunologie und Genetik, Deutsches Krebsforschungszentrum, Heidelberg, W. Germany); Bosslet, K.; Shantz, G.; Clauer, K.; Hubsch, D. *Int J Cancer* 23(2): 245-252; 1979.

The syngeneic cytotoxic T-cell response against a metastasizing murine lymphoma variant (ESb) was investigated and compared with the response against the nonmetastasizing parental tumor line Eb. Antitumor cytotoxicity (ATC) was not detectable in a 4-hr ^{51}Cr -release assay in spleens taken directly from tumor-bearing animals [primary cell-mediated cytotoxicity (CMC)]. After restimulation in vitro (secondary CMC), however, high ATC was detected. This activity was mediated by immune T lymphocytes, as shown by its sensitivity to treatment with anti-Thy 1.2 serum and complement. Ten cells of the metastasizing tumor ESb, inoculated sc, were sufficient to raise a local tumor and metastases and to induce cytotoxic T memory cells in the spleens. In contrast, about 10^4 Eb cells were required to raise a local tumor and to induce splenic cytotoxic T memory cells. Specificity studies of the ATC demonstrated that cytotoxic T cells could distinguish unrelated, chemically induced syngeneic tumors and also recognize antigenic differences between the parental tumor Eb and its variant ESb. Eb and ESb tumor cells were recognized as carrying distinct antigens at the responder cell level, the stimulator cell level, and the target cell level. The in vivo significance of these findings is discussed. (47 refs)

- 79-1658 Tumor-Specific Leukocyte Adherence Inhibition Responses of Mice with Moloney Murine Sarcoma Virus-induced Tumors (Meeting Abstract).** (Eng) Mortensen, R. F. (Michigan Cancer Foundation, Detroit, MI, 48201); Elson, L. *Fed Proc* 38(3, part 2): 1466; 1979. (no refs)

- 79-1659 Genetic Analysis of the Macrophage Tumoricidal Defect of A/J Mice (Meeting Abstract).** (Eng) Boraschi, D. (NIH, Bethesda, MD, 20014); Meltzer, M. S.; Doria, G. *Fed Proc* 38(3, part 2): 1288; 1979. (no refs)

- 79-1660 Pregnancy, Breast-Cancer Risk, and Maternal-Fetal Genetics (Letter to Editor).** (Eng) Janerich, D. T. (New York State Dept. Health, Cancer Control Bureau, Albany, NY, 12237). *Lancet* 1(8111): 327-328; 1979.

Evidence suggests that pregnancy may have adverse as well as beneficial effects on the risk of breast cancer. It is hypothesized that suppression of the immune system during pregnancy stimulates the growth of latent tumors, most of which are destroyed when the immune system returns to normal after pregnancy. Some tumors, however, may become too established during pregnancy to be destroyed afterward, resulting in the higher rate of breast cancer observed in married women aged 25-40 yr. (5 refs)

- 79-1661 Activated Macrophages Digest the Extracellular Matrix Proteins Produced by Cultured Cells.** (Eng) Jones, P. A. (Div. Hematology-Oncology, Childrens Hosp. of Los Angeles, 4650 Sunset Blvd., Los Angeles, CA, 90027); Scott-Burden, T. *Biochem Biophys Res Commun* 86(1): 71-77; 1979.

The degradation by activated mouse peritoneal macrophages of the extracellular matrix proteins produced by cultured smooth muscle cells was studied. The smooth muscle cells, obtained from culture passages 4-8, were incubated with ^3H -proline, which resulted in the synthesis of an extensive radioactively labeled matrix. The producer cells were removed from the culture dishes by mild alkaline treatment, and the activated macrophages were cultured on the matrix with various serum supplements. The digestion rate was dependent on the serum supplement, with the slowest degradation occurring under serum-free conditions and the most rapid in the presence of dog serum, which contains high levels of plasminogen (PMG). The presence of PMG caused a considerable stimulation of hydrolysis, especially under serum-free conditions with added PMG. The supernatant medium from dishes containing macrophages plated on ^3H -proline-labeled matrices was analyzed by Sephadex G-25 gel filtration. After 24 hr, a small amount of radioactivity eluted in the position in which ^3H -proline eluted from the column; the percentage of radioactivity in this position increased linearly with time. The results show the macrophages produce enzymes capable of digesting the matrix and that macrophage PMG activator has a major role in this digestion. (16 refs)

- 79-1662 Effects on In Vitro Tumor Growth of Macrophages Isolated from Human Ascitic Ovarian Tumors.** (Eng) Mantovani, A. (Istituto di Ricerche Farmacologiche "Mario Negri", Via Eritrea 62, 20157 Milan, Italy); Peri, G.; Polentarutti, N.; Bolis, G.; Mangioni, C.; Spreafico, F. *Int J Cancer* 23(2): 157-164; 1979.

Macrophages (MP's) were isolated from 22 human ascitic ovarian epithelial tumors, and their growth-inhibitory

capacity was tested using the following in vitro tumor cell lines as targets: murine TLX9 lymphoma and FS6 sarcoma; human myeloid K562 leukemia and a human E-cell line derived from an ovarian carcinoma. MP preparations were heterogeneous in their interaction with tumor target cells, and assay conditions, such as the type of target cell, incubation time, and attacker to target cell (A:T) ratio, critically affected the evaluation of the cytotoxic potential of tumor-associated MP's. At an A:T ratio of 7:1, no cytostatic activity on TLX9 and K562 cells was ever observed, but in the presence of specific antibody, 8/12 MP preparations tested showed significant antibody-dependent cytotoxicity on TLX9 lymphoma cells. MP preparations from two patients significantly inhibited growth of the FS6 sarcoma, and a cytostatic activity on E cells was observed in five additional patients. Significant stimulation of the proliferative capacity of at least one of the target cell lines was observed in 11 subjects at an A:T ratio of 7:1. In 12 patients, MP cytostatic activity on E cells was also tested at an A:T ratio of 35:1; 8/12 preparations showed significant cytotoxicity under these conditions. When the same subject was repeatedly tested at short intervals, the same pattern of inhibition or stimulation of tumor growth was observed. (35 refs)

79-1663 Resistance to Tumor Growth by Nude Mice (Meeting Abstract). (Eng) Haider, T. F. (State Univ. New York at Buffalo, Buffalo, NY, 14214); Flanagan, T. D.; Collins, A. R. *Fed Proc* 38(3, part 2): 1363; 1979. (no refs)

79-1664 Failure of Antineoplastic Immunosurveillance in Magnesium Deficient Rats (Meeting Abstract). (Eng) Hass, G. M. (Rush Univ., Chicago, IL, 60612); Laing, G. H.; McCreary, P. A.; Galt, R. M. *Fed Proc* 38(3, part 2): 1393; 1979. (no refs)

79-1665 Role of Non-H-2 Linked Genes in the Growth of L-1210 Ascites In Vivo (Meeting Abstract). (Eng) Wong, D. (Naval Medical Res. Inst., Bethesda, MD, 20014); Ahmed, A.; Strong, D. *Fed Proc* 38(3, part 2): 1289; 1979. (no refs)

79-1666 Studies on Immunity to Carcinogen-induced Transplantable Fibrosarcoma (SCFS) in SC Chickens (Meeting Abstract). (Eng) Galton, J. (New York Univ. Sch. Medicine, New York, NY, 10016); Palladino, M. A.; Thorbecke, G. J. *Fed Proc* 38(3, part 2): 1089; 1979. (1 ref)

79-1667 Enhancement Versus Tumor Resistance Induced by Different Levels of Immunodepression in BALB/c Mice with Protozoan Infections. (Eng) Landolfo, S. (Dept. Microbiology, Univ. Turin, Via Santena 9, 10126

Turin, Italy); Giovarelli, M.; Martinotti, M. G.; Varesio, L.; Cappuccinelli, P. *Eur J Cancer* 15(1): 27-33; 1979.

The relationship between the immunodepression induced by infection with *Trypanosoma congolense* (TC) or *Trichomonas vaginalis* (TV) and in vivo resistance to the growth of a spontaneous syngeneic mammary adenocarcinoma (ADK/lt) was evaluated in BALB/c mice. Mice were challenged with $\times 0.1$ ml of a suspension containing 10^8 sheep RBC 7, 20, 28, and 39 days postinfection (PI). The number of plaque-forming cells and the hemolytic and hemagglutinating antibody titers were reduced 12 days PI in TV-infected (TVI) mice. Thereafter, the response returned to control levels. TCI animals showed a marked decrease in all three parameters throughout the 10-wk experiment. At 8 days PI, all infected mice exhibited a marked depression of the cellular response to oxazolone compared with controls; however, a return to normal levels occurred on day 15 in TVI mice and on day 29 in TCI mice. The spleen cell response to phytohemagglutinin was depressed significantly between days 8 and 15 in both infected groups; however, normal levels were reached by day 22 in TVI mice vs day 29 in TCI mice. Tumor incidence and growth were evaluated in control and infected mice inoculated with 10^5 ADK/lt cells (1 wk PI in the latter). Initially, tumor incidence was slightly higher in TVI mice vs controls; this difference disappeared between 28 and 32 days after tumor injection when a 100% incidence occurred in both groups. Tumor growth rate and tumor mass were higher in TVI mice than in controls. In TCI animals, however, tumor take was much lower than that in controls and a 100% incidence was reached 18-20 days after it occurred in controls. Tumor growth in these mice was consistently slower than that in the other two groups. It is concluded that low or high levels of immunodepression, probably related to low or high levels of macrophage activation, appear to induce different patterns of tumor growth. (42 refs)

79-1668 Induction of Immunosuppressive Effects During Viral Leukemogenesis (Meeting Abstract). (Eng) Robinson, M. K. (Roswell Park Memorial Inst., Buffalo, NY, 14263); Manly, K. F.; Evans, M. J. *Fed Proc* 38(3, part 2): 1099; 1979. (no refs)

79-1669 A Histological Study of Spontaneous Regression of Cutaneous Melanomas in Domestic Swine (Meeting Abstract). (Eng) Stephens, E. C. (Sinclair Comparative Medical Res. Farm UMC, Columbia, MO, 65201); Middleton, C. C.; Adelstein, E. H.; Hook, R. R. *Fed Proc* 38(3, part 2): 1451; 1979. (no refs)

79-1670 Significance of Immunosuppression for Tumor Growth and Spread. (Ger) Dorschner, W. (Urologische Klinik, Karl-Marx-Universität Leipzig, Liebigstrasse 21, DDR-701 Leipzig, E. Germany); Schonfelder, M. *Z Urol Nephrol* 71(10): 747-752; 1978.

The effect of immunosuppression on the transplantability of human melanoblastoma and breast carcinoma cells was studied in male and female Wistar rats. The tumors cells (2×10^6 /animal) were transplanted iv, ip, or sc after immunosuppression was achieved by methotrexate (MTX: 1 mg/wk x 2, then 0.5-0.25 mg/wk, im; av total dose, 5 mg/animal). Some animals also received azathioprine (av total dose, 5 mg/animal) after tumor transplantation. The controls received MTX or tumor cells only. The animals were autopsied 2 days to 6 wk after tumor cell transplantation. Fifteen of 44 controls treated with MTX only died of infection or hemorrhage. These controls had severe signs of hepatotoxicity and nephrotoxicity, a depleted bone marrow, and a nearly complete absence of round cells in the spleen. The animals treated with MTX with and without azathioprine developed liver and lung metastases, but tumor growth lasted only as long as the immunosuppressive effect. The animals that did not receive immunosuppressive treatment did not develop tumors after transplantation. (no refs)

- 79-1671 Effector and Suppressor Lymphoid Cells in Tumor-bearing Guinea-Pigs.** (Eng) Berci, I. (Dept. Immunology, Univ. Manitoba, Winnipeg, Manitoba R3E OW3, Canada); Schon, A. H. *Int J Cancer* 23(2): 274-282; 1979.

The immune reaction of guinea pigs against their growing tumors was studied. Strain 13 guinea pigs were killed 2 wk after sc implantation of a transplantable methylcholanthrene-induced sarcoma (MC-D), when the tumor was 2-3 cm in diameter. Spleen, lymph node, and bone marrow cells, peripheral blood leukocytes (PBL), and subsets of spleen cells and PBL were mixed with lethal doses (10^5) of tumor cells and inoculated sc into normal recipients. Spleen, lymph node, and bone marrow cells either enhanced or did not influence tumor growth, but PBL exerted a strong inhibitory effect. Normal spleen and normal PBL did not affect tumor growth. The spleen cells of tumor-bearing animals were separated on nylon wool columns: the first fraction containing T cells was responsible for tumor enhancement, the second fraction containing predominantly non-T (Ia+) cells inhibited tumor growth. Adherent cells had no effect. Similarly, after removal of T cells from the spleens with a specific rabbit antiserum or of non-T cells plus a minor portion of T cells with an anti-Ia serum (produced in strain 2 guinea pigs), the remaining cell population had, respectively, an inhibitory or an enhancing effect on tumor growth. By contrast, removal of either T or Ia+ cells from PBL eliminated their antitumor effect. The major portion of splenic T cells formed erythrocyte-antibody (EA) rosettes. EA rosette-positive cells were restricted to a minor portion of the peripheral T lymphocytes. Thus, splenic and peripheral T cells from tumor-bearing animals were different both functionally and according to their surface markers. Fc+ T cells are hypothesized to be suppressors that are triggered by immune complexes. (42 refs)

- 79-1672 C-Type Virus Immunosuppression: Restoration of Abnormal Lymphocyte Con A Receptor Mobility (Meeting Abstract).** (Eng) Nichols, W. S. (Dept. Pathology, Ohio State Univ., Columbus, OH, 43210); Dunlap, J. E.; Hebebrand, L. C.; Mathes, L. E.; Olsen, R. G. *Fed Proc* 38(3, part 2): 1425; 1979. (no refs)

- 79-1673 In Vitro Activation of Cytotoxic Effector Cells from Tumor Bearing Mice (Meeting Abstract).** (Eng) Geliebter, J. (State Univ. New York, Downstate Medical Center, Brooklyn, NY, 11203); Howe, M. *Fed Proc* 38(3, part 2): 1214; 1979. (no refs)

- 79-1674 Immunoglobulin-producing Cells in the "Transitional" Mucosa Adjacent to Adenocarcinomas of the Human Large Bowel.** (Eng) Rognum, T. O. (Histological Lab., Inst. Pathology, University Hosp., Oslo, Norway); Brandtzaeg, P.; Baklien, K.; Hognestad, J. *Int J Cancer* 23(2): 165-173; 1979.

IgA-, IgM-, and IgG-producing immunocytes were quantitated in a defined mucosal tissue unit adjacent to 16 adenocarcinomas of the large bowel, and the data were compared with data for control units from 15 histologically normal specimens. The thickness of the "transitional" mucosa adjacent to the tumors was markedly increased. Thus, the av cancer-associated unit showed a 2.6-fold increase in height and its number of immunoglobulin-producing cells was raised 2.8 times. The numerical increase for IgA cells was 2.1, for IgM cells 5.1, and for IgG cells 13.0; the percentage proportions of these cell classes were changed from 91:6:3.6 to 71:12:17. Only very rare IgD- and IgE-producing cells were seen. The immunocyte density in 6- μ m-thick sections (cell number/mm² of lamina propria) was 823, 136, and 201 for the IgA, IgM, and IgG class, respectively, compared with the normal figures of 1,186, 73, and 49. The density of IgG and IgM cells was thus significantly increased and that of IgA cells decreased in the lamina propria of the "transitional" mucosa. The intraindividual scatter of all variables, including mucosal height, was large in the "transitional" mucosa, but the variables became normalized approx 1 cm from the tumor. The excessive rise in the local production of IgG, with no concomitant increase in the density of IgA cells, indicates that there are local stimulatory factors bypassing the secretory IgA immune system. Further studies are needed to show if this local immune response reflects the production of tumor-specific antibodies or is merely due to the increased penetrability of antigens from the gut lumen through the tumor lesion. (35 refs)

- 79-1675 Systemic Lupus Erythematosus and DNA Antibodies in Pleural Effusions.** (Eng) Riska, H. (Mjølbolsta Hosp., 103 50 Mjølbolsta, Finland); Fyhrquist, F.; Selander, R. K.; Hellstrom, P. E. *Scand J Rheumatol* 7(3): 159-160; 1978.

High binding of double-stranded DNA was observed in pleural fluid from five patients with systemic lupus erythematosus (SLE) and four with lung cancer. However, DNase treatment revealed that DNA-anti-DNA complexes in pleural fluid were confined to the SLE patients and were not present in pleural fluid from lung cancer patients. (5 refs)

79-1676 Human Brain Tumor Transplantation into Nude Mice. (Eng) Shapiro, W. R. (George C. Cotzias Lab. Neuro-Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021); Basler, G. A.; Chernik, N. L.; Posner, J. B. *J Natl Cancer Inst* 62(3): 447-453; 1979.

Seven human brain tumors were transplanted into the brains (6/7 takes) and sc tissues (7/7 takes) of inbred Swiss athymic nude mice. Compared with experimental animal brain tumors, these tumors, taken directly from patients in the operating room and transplanted, grew more slowly in the mice. Their growth rates following explant generally paralleled those in the patients. A rough correlation was seen between degree of tumor malignancy and both successful take rate and rate of growth following explant. Growth rates increased during serial transplantation after explant. Two tumors developed into long-term serial lines; both came from gliosarcomas. Preliminary chemotherapy experiments with these two lines demonstrated differential chemosensitivities. One line was very sensitive to several nitrosoureas and resistant to procarbazine; the other was more sensitive to procarbazine than to the nitrosoureas. This model permits study of the biologic behavior of human brain tumors growing intracerebrally and sc in nude mice. (20 refs)

79-1677 A Genetic Basis for the Susceptibility of Rabbits to the VX2 Tumor (Meeting Abstract). (Eng) Lancki, D. W. (Univ. Illinois Medical Center, Chicago, IL, 60680); Tissot, R. G.; Cohen, C. *Fed Proc* 38(3, part 2): 1104; 1979. (no refs)

79-1678 The Presence of F9 Antigen on the Surface of Mouse Embryonic Cells Until Day 8 of Embryogenesis. (Eng) Buc-Caron, M. H. (Service de Genetique cellulaire, College de France, Institut Pasteur, 25 rue de Dr Roux 75015, Cedex 15, Paris, France); Condamine, H.; Jacob, F. *J Embryol Exp Morphol* 47: 149-160; 1978.

The presence of F9 antigen on the cell surface of mouse embryos was examined by anti-F9 serum absorption and indirect immunofluorescence staining tests. Pregnant strain 129/Sv mice were killed on day 7, 8, or 9 of pregnancy, and embryonic cell suspensions were prepared. F9 antigen was readily detected by both methods on the surface of 7- and 8-day-old embryonic cells but not on 9-day cells. An anti-F9 serum that absorbed with 8-day (but not with 9-day) embryonic cells did not react with 2-day embryos (morulae). The major histocompatibility (H-2) antigen was demonstrable on 9-day

cells but not on 8-day cells. In immunofluorescence staining experiments, labeling occurred in >95% of the cells from 7-day embryos, 58% of the cells from 8-day embryos, and essentially none from 9-day embryos. It is concluded that the antigenic determinants that are recognized on the surface of morulae by the anti-F9 serum are also present on 8-day embryos but not on 9-day embryos. They are either absent, masked, or quantitatively reduced. (24 refs)

79-1679 Control of Oncofetal Antigen Production as an Epiphenomenon of Tumorigenesis (Meeting Abstract). (Eng) Yoo, T. J. (Dept. Medicine, Univ. Iowa, Iowa City, IA); Kuo, C.; Patil, S.; Kim, U.; Ackerman, L.; Cancilla, P.; Chiu, H. C. *Fed Proc* 38(3, part 2): 918; 1979. (no refs)

79-1680 Remission of Myelogenous Leukemia in Pregnant Rats (Meeting Abstract). (Eng) Hass, G. M. (Rush Univ., Chicago, IL, 60612); Laing, G. H.; McCreary, P. A.; Galt, R. M. *Fed Proc* 38(3, part 2): 1274; 1979. (no refs)

79-1681 Mechanism of Immune Suppression During Reticuloendotheliosis Virus (REV)-induced Acute Leukemia: Role of the Non-Oncogenic Helper in the Suppression (Meeting Abstract). (Eng) Rup, B. (Univ. Texas, Austin, TX, 78712); Carpenter, C.; Hoelzer, J.; Kroen, S.; Lewis, R.; Bose, H.; Rubin, A. *Fed Proc* 38(3, part 2): 1274; 1979. (1 ref)

79-1682 Binding Patterns of IgG Molecules Eluted from Leukocytes of Leukemia Patients (Meeting Abstract). (Eng) Witz, I. P. (NIH, Bethesda, MD, 20014); Ganguly, A.; Jacquemin, P.; Gallo, R. C. *Fed Proc* 38(3, part 2): 1160; 1979. (1 ref)

79-1683 Characterization of a Leukemic Cell Line of the Pre-B Phenotype. (Eng) Hurwitz, R. (Dept. Pediatrics, Univ. Minnesota, Minneapolis, MN, 55455); Hozier, J.; LeBien, T.; Minowada, J.; Gajl-Peczalska, K.; Kubonishi, I.; Kersey, J. *Int J Cancer* 23(2): 174-180; 1979.

The characteristics of NALM-6-M1, one of eight leukemia cell lines cultured from the peripheral blood of a 19-yr-old boy with non-T, non-B acute lymphoblastic leukemia in relapse, are presented. This cell line was found to be >90% cytoplasmic immunoglobulin positive (cIg+) for both mu heavy and lambda light chains, but surface immunoglobulin and complement receptor negative. NALM-6-M1 was cIg- for alpha, delta, and gamma heavy chains and kappa light chain. About 45% of the cells exhibited sheep RBC receptors. Approx 12% of the cells were positive for Fc receptors. Approx 90% of the cultured cells had a deleted long arm of chromosome 5 (5q-) and a marker Y chromosome. The remaining 10% of cells had some additional chromosomal

material on the long arm of chromosome 12, suggesting a partial translocation. No other karyotypic abnormalities were found. The cell line reacted strongly with anti-p23,30, suggesting Ia-like activity, but it only weakly stimulated normal lymphocytes in mixed leukocyte culture. The cells expressed HLA antigens. NALM-6-M1 failed to react with anti-thymocyte serum, did not possess Epstein-Barr membrane or nuclear antigens, and did not exhibit phagocytosis for zymosan. NALM-6-M1 reacted positively with Oil Red O and Sudan black stains. The cIgM staining indicates that NALM-6-M1 is arrested at an early stage in B-cell development. This cell line is considered to be of the pre-B-cell phenotype possessing a chromosomal abnormality. (27 refs)

- 79-1684 Idiopathic Paraproteinemia. II. Transplantation of the Paraprotein-producing Clone from Old to Young C57BL/KaLwRij Mice.** (Eng) Radl, J. (Inst. Experimental Gerontology of the Organization Health Res. TNO, 151, Lange Kleiweg, Rijswijk, Netherlands); De Glopper, E.; Schuit, H. R.; Zurcher, C. *J Immunol* 122(2): 609-613; 1979.

Bone marrow and/or spleen cells from old C57BL mice with idiopathic paraproteinemia (IP) were transplanted into young syngeneic mice with a normal heterogenous immunoglobulin pattern to determine whether factors intrinsic or extrinsic to the immune system and to the paraprotein-producing cell clone are responsible for IP. In 9/10 experiments, the IP-producing clone "took" in the recipients. The take frequency was the same in irradiated and nonirradiated recipients, but the paraprotein was generally detected 1-3 mo earlier in the irradiated mice. Cells from the mesenteric lymph node of a mouse with IP were less efficient in inducing IP in normal recipients, and the cell-free extract of bone marrow or spleen cells was not effective. Propagation of IP for three to four transplant generations seemed to be the final limit: the av take frequency for generations 1-4 was 63%, 51%, 23%, and 4%, respectively. Transplantation of cells from mice with a lymphoreticular malignancy resulted in a continuous propagation of the malignancy, with a high take frequency, progressive development of the paraproteinemia, and a shortened recipient survival time. The data indicate that IP represents in its final stage in the aging C57BL mouse, an intrinsic defect within the affected B-cell clone and that this defect differs from that found in B-cell malignancies. (16 refs)

- 79-1685 Tumor Induction in Host-vs-Graft Disease (HVGD) II. Immunologic and Virologic Features (Meeting Abstract).** (Eng) Cornelius, E. (Yale Univ., New Haven, CT, 06510). *Fed Proc* 38(3, part 2): 992; 1979. (no refs)

- 79-1686 Establishment and Characterization of BALB/c Lymphoma Lines with B Cell Properties.** (Eng) Kim, K. J. (Lab. Microbial Immunity, Natl. Inst. Allergy and Infectious Diseases, NCI, NIH, Bethesda, MD, 20014);

Kanellopoulos-Langevin, C.; Merwin, R. M.; Sachs, D. H.; Asofsky, R. *J Immunol* 122(2): 549-554; 1979.

Five spontaneously derived BALB/c tumors (K46, X16C, L10A, A20, and M12) and one 1-ethyl-1-nitrosourea-induced BALB/c tumor (BALENLM 17) were established in culture and characterized according to their surface markers. L10A, X16C, K46, and BALENLM 17 were found to bear IgM, Fc receptors, and I-region-associated (Ia) antigens. A20 expressed Fc receptors and Ia antigens, and M12 had only Fc receptors. All lines bore surface immunoglobulin (Ig) and none bore complement receptors. Although all lines stained with intact molecules or with F(ab')₂ fractions of polyvalent anti-mouse Ig antibodies, staining of M12 with these agents was faint. None of the six lines phagocytized latex particles, all were negative for Thy 1.2 antigen, and they grew as stationary suspension cultures. Therefore, these six BALB/c lymphoid lines are presumably of B-cell origin at various stages of differentiation. The chromosome numbers of L10A, K46, and X16C were hypotetraploid, whereas those of BALENLM 17, A20, and M12 were near diploid. The generation times of the lines ranged from 18 to 26 hr. After > 6 mo in culture, all cell lines except X16 were tumorigenic in BALB/c mice within 1 mo. (40 refs)

- 79-1687 Tumor Metastases and Cell-mediated Immunity in a Model System in DBA/2 Mice. I. Tumor Invasiveness In Vitro and Metastasis Formation In Vivo.** (Eng) Schirmacher, V. (Institut für Immunologie und Genetik, Deutsches Krebsforschungszentrum, Heidelberg, W. Germany); Shantz, G.; Clauer, K.; Komitowski, D.; Zimmermann, H. P.; Lohmann-Matthes, M. L. *Int J Cancer* 23(2): 233-244; 1979.

Tumor metastases and cell-mediated immunity were studied in a syngeneic model system in DBA/2 mice. The system consisted of two related methylcholanthrene (MC)-induced murine lymphomas, the nonmetastasizing parental line Eb and its metastasizing variant ESb. An unrelated MC-induced tumor (MDAY) was included for specificity controls. Serological typing revealed that Eb and ESb were of T-lymphoid origin and that they expressed the H-2K and H-2D molecules of the host strain (DBA/2). By various electron microscope techniques, morphological differences were observed between the two cell lines. ESb tumor cells had a more polymorphic nucleus with many invaginations of the nuclear envelope and a more prominent expression of microvilli on the cell surface. An in vitro organ culture test for tumor invasiveness, presented here for the first time in a syngeneic murine system, revealed that ESb but not Eb cells had the ability to attach to and invade normal tissue. Accordingly, ESb cells showed higher malignancy in vivo. This was apparent from their higher tumorigenicity and their ability to disseminate and metastasize and to kill recipient mice more quickly. Upon histological examination of the local primary tumors, a striking difference was noticed with regard to the degree of infiltration by host-derived mononuclear cells, mostly histiocytes. The nonmetastasizing tumor Eb was heavily infiltrated, but

tumor ESb contained only a few of these cells. The differences between ESb and Eb are considered in the light of their possible relevance for metastases in general. (46 refs)

79-1688 Protein Patterns of Normal and EBV-Genome Positive Human B Lymphocytes (Meeting Abstract). (Eng) Bachvaroff, R. J. (Dept. Surgery, State Univ. New York at Stony Brook, Stony Brook, NY, 11594); Rapaport, F. T. *Fed Proc* 38(3, part 2): 1369; 1979. (no refs)

79-1689 Discordance of Epstein-Barr Virus (EBV) Specific Humoral and Cellular Immunity in Patients With Malignant Lymphomas: Elevated Antibody Titres and Lowered In Vitro Lymphocyte Reactivity. (Eng) ten Napel, C. H. (Dept. Medicine, Univ. Hosp., Oostersingel 58, Groningen, Netherlands); The, T. H.; Van Egten-Bijker, J.; De Gast, G. C.; Halie, M. R.; Langenhuisen, M. M. *Clin Exp Immunol* 34(3): 338-346; 1978.

The relationship between specific viral cellular and humoral immunity to Epstein-Barr virus (EBV) was studied in 17 untreated patients with Hodgkin's disease (HD: age 9-61 yr; median 30), 14 untreated patients with non-Hodgkin's lymphoma (age 21-81 yr; median 59), and 31 age- and sex-matched healthy controls. Antibodies to EBV virus capsid antigens (EBV-VCA) were present in 29/31 malignant lymphoma (ML) patients, and all controls were seropositive. The geometric mean titer (GMT) was markedly higher in the HD patients (3,180) than in the controls (924). The GMT of the non-Hodgkin's lymphoma patients was not significantly raised compared with that of controls (1,424 vs 861). EBV-induced lymphocyte reactivity (EBV-LR) was markedly lower in the ML patients, especially those with HD, than in the controls. Ten of 13 of the controls with EBV-VCA antibody titers > 640 were positive for EBV-LR, compared with only 30% of the ML patients and 30% of the HD pa-

tients. LR to antigen cocktail (containing diphtheria and tetanus toxins, *Candida albicans* antigens, and purified protein derivative) and mitogen stimulation was lower in ML patients than in controls, but most patients showed responses within the normal range. There was no correlation between LR to EBV and general LR to antigens and mitogens. General LR did not differ in EBV-seropositive patients with positive EBV-LR and those with negative EBV-LR. The results support the hypothesis that depressed cellular immunity may cause raised EBV antibodies in ML, especially in HD. (33 refs)

79-1690 Immunosuppression Enhances Sinclair Swine Melanoma Growth (Meeting Abstract). (Eng) Berkelhammer, J. (Cancer Res. Center, Columbia, MO, 65201); Caines, S. M.; Aultman, M. D.; Hook, R. R. *Fed Proc* 38(3, part 2): 1176; 1979. (no refs)

See also:

*(Rev.): 79-1216, 79-1250, 79-1258, 79-1259, 79-1260, 79-1261, 79-1265.

*(Chem.): 79-1375, 79-1412, 79-1423, 79-1464.

*(Viral): 79-1541, 79-1550, 79-1551, 79-1555, 79-1558, 79-1567, 79-1569, 79-1571, 79-1572, 79-1575, 79-1576, 79-1577, 79-1578, 79-1579, 79-1584, 79-1489, 79-1591, 79-1600, 79-1615, 79-1616, 79-1635, 79-1636, 79-1638, 79-1639, 79-1641, 79-1645, 79-1646, 79-1648, 79-1650.

*(Path.): 79-1726.

*(Epid.-Biom.): 79-1772, 79-1775, 79-1778.

- 79-1691 Sex Chromosome Aberrations Involving Loss and Translocation of Tumor-inducing Loci in *Xiphophorus*. (Eng) Ahuja, M. R. (Genetisches Institut, Justus-Liebig-Universität Giessen, Heinrich-Buff-Ring 58-62, D-6300 Giessen, W. Germany); Lepper, K.; Anders, F. *Experientia* 35(1): 28-30; 1979.

The cytologic nature of (1) a deletion involving the Sd (spotted dorsal fin) locus and (2) an X-Y translocation involving the Sr (striped sides of body) locus of the platyfish, *Platyplecillus* (*Xiphophorus*) *maculatus*, was investigated, along with the genetic consequences of these aberrations on the tumor potential and viability of the fish. Analysis of the Sd deletion revealed a loss of one of two major terminal Giemsa bands of the X-chromosome. The fragment lost due to deletion was approx 0.3-0.5 μ m long, or up to one-quarter of the chromosome. The genetic consequences of this deletion are that neither males nor females exhibit black spots on the dorsal fin and they do not develop melanomas on the dorsal fin after exposure to a chemical carcinogen. Karyotypic analysis of the X-Y translocation revealed that the Sr fragment is probably translocated to the end of the normal arm of the X-chromosome. The phenotypic consequence of this translocation is that both sexes are stripe-sided. Females do not develop melanomas, suggesting that the controlling gene that governs the expression of Sr is translocated along with Sr and closely linked to it. Impairment or deletion of tissue-specific regulating genes presumably leads to neoplasia, whereas loss or impairment of the tumor-inducing loci (eg, Sr or Sd) would lead to loss of tumor-inducing potential in a specific tissue. (19 refs)

- 79-1692 Karyotypic Evolution Associated with Loss of Tumorigenicity. (Eng) Shepard, J. S. (Dept. Pathology, Dartmouth Medical Sch., Hanover, NH, 03755); Pettengill, O. S.; Wurster-Hill, D. H.; Sorenson, G. D. *J Natl Cancer Inst* 62(3): 547-554; 1979.

The karyotypes and tumorigenicities (TG's: in normal and irradiated BALB/c mice) of two cell culture lines (SLU-5 and DMS-402) established from the mouse plasmacytoma MOPC-21 carried in BALB/c mice were followed for up to 70 mo after isolation. After 36 mo, SLU-5 cells were non-TG in normal BALB/c mice but were still TG in irradiated mice; by 64 mo, the culture was nonlethal in irradiated hosts. Although the number of chromosomes in this culture remained constant during 70 mo, each loss of TG was associated with a change in karyotype. Similar changes in karyotype and TG were observed in DMS-402, although TG decreased after 17 mo in culture. The data suggest that the cultures were heterogeneous and that new cell populations arose because of selection for cell types already present in the young cultures. Whe-

reas most markers remained constant in appearance during the culture period, m10 underwent successive intrachromosomal alterations, one for each qualitative change in TG. These marker changes were small and cryptic, were not easily explained as translocations, and looked more like specific regional alterations in chromosome coiling. The presumed original defect in chromosome 15, which has been specifically associated with mouse myelomas, was not corrected or eliminated when TG was lost. In conclusion, loss of TG was not an all-or-none phenomenon but a gradual or incremental process, and each change of potency was the outcome of natural selection for a new cell type. (20 refs)

- 79-1693 Transformation of Normal Diploid Cells by Isolated Metaphase Chromosomes of Virus-transformed or Spontaneous Tumor Cells. (Eng) Cassingena, R. (Institut de Recherches Scientifiques sur le Cancer, B.P. No. 8, 94800-Villejuif, France); Suarez, H. G.; Lavialle, C.; Persuy, M. A.; Ermonval, M. *Gene* 4(4): 337-349; 1978.

The in vitro transformation of a variety of normal diploid cells (human embryonic lung, Swiss mouse embryo, Wistar rat embryo) by metaphase chromosomes (CS's) isolated from various virus-transformed or spontaneous tumor cells was examined. The CS donors included cells from (1) human skin transformed by simian virus 40 (SV40), (2) WAG rat embryonic lung transformed by SV40, (3) human embryonic kidney transformed by sheared adenovirus 5 DNA, (4) A/Jax mouse neuroblastoma, and (5, 6, 7) human cervical carcinoma, lung carcinoma, and melanoma. Approx $1-3 \times 10^6$ recipient cells were mixed with $2-6 \times 10^7$ isolated CS's. After exposure to CS's from any of the three virus-transformed lines, both homologous and heterologous recipient cells were able to form colonies in selective soft agar and/or low serum medium. Colonies appeared with a frequency of 10^{-4} - 10^{-6} , the highest being observed in intraspecific transfers with CS's from SV40-transformed cells. When normal diploid cells were exposed to CS's from mouse or human tumor cells, every combination gave rise to colony formation in selective medium, with frequencies of 10^{-3} - 10^{-6} . CS's from normal diploid cells did not show any transforming activity. In general, transformation efficiency was higher for homologous than for heterologous transfers. A fraction of the colonies stopped growing and died after the third week. Nevertheless, using CS's from all but one donor cell population (human melanoma), at least one transformed cell line expressing a stable transformed phenotype was established. The results show that normal diploid cells can be transformed by a presumptive CS-mediated gene transfer with a variety of donor and recipient cells. (21 refs)

PATHOGENESIS

- 79-1694 Risk of Malignancy and Chromosomal Polymorphism: A Possible Mechanism of Association.** (Eng) Shabtai, F. (B. Gattegno Res. Inst. Human Reproduction and Fetal Development, Hasharon Hosp., Petah-Tiqva, Israel); Halbrecht, I. *Clin Genet* 15(1): 73-77; 1979.

The possible association of heterochromatic chromosomal variants and risk of malignancy was investigated in 120 patients (62 men, 58 women aged 14-78 yr) with malignant or premalignant hematologic diseases. The group comprised 30 patients with different types of acute leukemia, 20 with chronic myelocytic leukemia, 17 with polycythemia rubra vera, and 53 with a series of aplastic, hyperplastic, dysplastic, and metaplastic disorders and considered to be in a preleukemic state. The results were compared with those of two other studies and with the findings for two groups of newborns ($n = 500$ and 800 , respectively). There was a statistically significant increase in the incidence of the major heterochromatic variants, ie, A_1 and C_2 , in the 120 patients compared with the four control groups. Although most of the patients were untreated at the time of examination, an increased chromosome breakage rate was a frequent finding, and it was almost always connected with the presence of heterochromatic variants. A genetically increased susceptibility to breaking agents may explain the increased incidence of heterochromatic variants found in patients with malignant or premalignant diseases. Chromosome imbalance is probably the basis for initiation of malignancy, whose development is influenced by many different factors. (25 refs)

- 79-1695 Occurrence and Significance of Chromosome Aberrations in Malignant Cells (Meeting Abstract).** (Eng) Levan, G. (Dept. Genetics, Univ. Gothenburg, Gothenburg, Sweden). *Heredity (Lond)* 41(part 3): 416; 1978. (no refs)

- 79-1696 K562--A Human Erythroleukemic Cell Line.** (Eng) Andersson, L. C. (Transplantation Lab., Univ. Helsinki, Helsinki, Finland); Nilsson, K.; Gahrberg, C. G. *Int J Cancer* 23(2): 143-147; 1979.

The surface membrane properties of the Philadelphia chromosome-positive human leukemic cell line K562, derived from a patient with chronic myeloid leukemia (CML) in acute blast crisis, were studied. Samples of surface-labeled (using the galactose oxidase- NaB^{14}H , method) normal RBC, K562 cells, HL-60 myeloid cells, normal granulocytes, and cells from patients with CML and acute promyelocytic leukemia were run in parallel slots on the same slab gel. The glycoprotein pattern of K562 showed striking similarities with that of the RBC, but it was completely different from the patterns of the other cells. Gp42 was strongly expressed on K562 cells, and it corresponded in electrophoretic mobility to the monomer of glycophorin (GPN). K562 cells incubated in the cold with the F(ab), preparation of the anti-GPN antiserum and fluorescein isothiocyanate-conjugated

sheep anti-rabbit Ig anti-serum showed a strong membrane fluorescence, as did normal RBC. After incubation of stained cells for 30 min at 37 C, a partial redistribution of the label was seen in some cells, indicating that the anti-GPN antiserum reacts with integral membrane protein(s) of K562 cells. Expression of GPN on the surface of K562 cells was also shown by immunoprecipitation from labeled membrane preparations. Since GPN is exclusively found on erythroid cells in human bone marrow, it is concluded that K562 is a human erythroleukemic line. The observed erythroid features of K562 suggest that, during blast crisis, the neoplastic stem cell has the potential to differentiate not only to immature myeloid or lymphoid cells, but also to erythroid cells. (28 refs.)

- 79-1697 B Cell Acute Lymphoblastic Leukemia (ALL) with a 14q+ Chromosome Abnormality.** (Eng) Roth, D. G. (Univ. Chicago Hosps., Box 420, 950 E. 59th St., Chicago, IL, 60637); Cimino, M. C.; Variakojis, D.; Golomb, H. M.; Rowley, J. D. *Blood* 53(2): 235-243; 1979.

The case report of a 33-yr-old man with acute lymphoblastic leukemia (ALL) associated with the 14q+ marker chromosome is presented. The abnormality resulted from a translocation of material from the long arm of chromosome 11: t(11;14)(q23;q32). The circulating leukemic cells had surface immunoglobulin, a lack of receptors for sheep RBC, and a low level of adenosine deaminase activity, characteristic of B cells. The finding of the 14q+ chromosome is of particular interest because this marker has been reported in only one other case of ALL, which was also a B-cell type. These are the only two cases of B-cell ALL known in which karyotype studies were done with banding techniques. The karyotype in the previous case, although less complex, had other features in common with the present case: an additional No. 7, a loss of No. 13, and a 6p+ rearrangement. The frequent occurrence of the 14q+ chromosome in other malignant lymphoproliferative diseases of B-cell origin suggests that this abnormality may be associated with B-cell neoplasms. The data show the value of cytogenetic studies in identifying discrete variants of hematologic diseases and in relating specific cytogenetic abnormalities with particular syndromes. (25 refs)

- 79-1698 Acute Myeloblastic Leukemia and Non-Hodgkin Lymphoma (Letter to Editor).** (Eng) Lonnqvist, B. (Medicinkliniken, Karolinska Institutet, 141 86 Hud-dinge, Sweden); Lockner, D. *N Engl J Med* 300(7): 367-368; 1979.

The case of a 67-yr-old man who simultaneously presented with a lymphocytic-lymphoblastic retroperitoneal lymphoma and an acute myeloblastic leukemia with Auer rods is reported. The patient had never received x-ray treatment or cytostatic therapy. (15 refs)

- 79-1699 Acute Myelogenous Leukaemia Occurring at the Same Time in Husband and Wife.** (Eng) Ly,

B. (Medical Dept. A, Rikshospitalet, Oslo, Norway); Stavem, P.; Saltvedt, E. *Scand J Haematol* 21(5): 376-378; 1978.

Acute myelogenous leukemia (AML) was diagnosed within 1 wk in a married Norwegian couple (husband aged 40, wife aged 31) without consanguinity. The husband had acute myelomonocytic leukemia, the wife classical-type AML. The husband, a previously healthy salesman, had swollen gums with recurrent and painful ulcerations for 1 yr prior to diagnosis. Three years prior to diagnosis, the wife had complained of pain and stiffness in several joints, symptoms that gradually subsided without treatment. Their histories revealed no cases of malignant blood disorders in their families and no exposure to x-rays, alkylating agents, or benzene and its derivatives. They lived in their own house in a small rural community, and their two children were in good health. In Norway, the probability for a married couple to develop AML within the same year is approx 1:400 million. If a common etiological factor had been involved, it certainly led to quite a different morphologic expression. (7 refs)

79-1700 Inbreeding, Lymphoma, Genetics and Morphology of the *Papio hamadryas* Colony of Sukhumi. (Eng) Crawford, M. H. (Lab. Biological Anthropology, Univ. Kansas, Lawrence, KS, 66044); O'Rourke, D. H. *J Med Primatol* 7(6): 355-360; 1978.

A preliminary report of visits to the Sukhumi Primate Center, USSR, which houses a colony of *Papio hamadryas* baboons that are infected with human lymphoma, is given. Examination of the pedigrees of the hamadryas population indicated that inbred baboons were at greater risk of contracting lymphoma than animals captured in the wild and that the disease was concentrated in certain lineages. Blood samples, morphological data, and complete pedigrees are being analyzed to explore the interactions between genetic and environmental factors in the etiology of lymphoma. (12 refs)

79-1701 Post-Capillary Venules in the Lymphatic Tissues of Mice Bearing Experimental Neoplasia. (Eng) Syrjanen, K. J. (Dept. Pathology, Jorvi Hosp., SF-02740 Espoo 74, Finland). *Exp Pathol (Jena)* 15(6): 348-354; 1978.

Light microscopy was used to study morphologic changes in the postcapillary venules (PCV's) of the lymph nodes, thymus, and Peyer's patches of normal DBA/2 mice and mice bearing mastocytomas. Some of the mice were treated sc with anti- θ -globulin prior to tumor cell inoculation. Three classes of PCV's were differentiated according to the height of the endothelial cells of the vessels. The highest mean PCV scores for lymph nodes and Peyer's patches were observed in normal mice, the scores in tumor-bearing mice being significantly lower. The scores of the tumor-bearing mice did not differ significantly from those of the tumor-bearers pretreated with anti- θ -globulin. PCV scores of the thymuses were low and did not differ significantly between normal and

tumor-bearing mice. Thus, a direct correlation seems to exist between the degree of T-cell depletion and the morphology of the PCV's in lymph nodes and Peyer's patches. The data support the concept that the structural state of the PCV endothelium is an important regulator of T-lymphocyte recirculation in nodes and Peyer's patches. (21 refs)

79-1702 Ultrastructural Organization of Thrombocytes in Normal Monkeys (*Macaca arctoides*) and in Those with Experimental Viral Malignant Lymphoma. (Eng) Chuvirov, G. N. (Institute Experimental Pathology and Therapy, USSR Acad. Medical Sciences, Gora Trapetziya, P.B. 66, Sukhumi, USSR); Fomenko, V. N. *Exp Pathol (Jena)* 15(6): 319-323; 1978.

The ultrastructure of the thrombocytes of healthy *Macaca arctoides* monkeys and monkeys with viral malignant lymphoma induced by inoculation with leukemic human blood was compared. The inner structure of the thrombocytes from the healthy monkeys was similar to that of normal human thrombocytes. The first ultrastructural changes in the thrombocytes for the lymphoma-bearing monkeys appeared 20 days after inoculation, almost simultaneously with the appearance of the first clinical symptoms. By the 60th day, elongated platelet forms were reduced to 80%-85% of the initial number and there was a 15%-20% increase in the number of gigantic roundish thrombocyte forms. The number of alpha, beta, and sigma granules was decreased, whereas the number of glycogen granules was increased. The size of the delta granules also increased. These changes may have resulted from the effects of the leukemic process on cell function and on the bone marrow megakaryocytes. Viral particles were not found in the thrombocytes of any sick monkey. (22 refs)

79-1703 Trisomy #15 in Murine Thymomas Induced by Chemical Carcinogens, X-Irradiation, and an Endogenous Murine Leukemia Virus. (Eng) Chan, F. P. (Dept. Anatomy, Univ. Western Ontario, London, Ontario, Canada N6A 5B7); Ball, J. K.; Sergovich, F. R. *J Natl Cancer Inst* 62(3): 605-610; 1979.

Chromosome banding techniques were used to examine the karyotype of tumor cells from thymic lymphomas induced in two low-leukemia mouse strains (CFW/D and C57Bl/Ka) (x-irradiation, polycyclic aromatic hydrocarbons, and an endogenous leukemogenic virus). Treatment consisted of 400 rads of x-radiation, injection of 40 μ 7,12-dimethylbenz(a)anthracene (DMBA) or 150 μ g benzo(a)pyrene, or injection of a DMBA-induced leukemia virus into a newborn mouse thymus placed under the kidney capsule of a normal 6-wk-old adult mouse. A total of 89 tumors were studied, and of these 85.4% were characterized by a modal chromosome number of 41. The additional chromosome was the result of a specific abnormality identified as trisomy of chromosome 15. The results were independent of the carcinogenic agents and the strain of mouse used. Of the 13 tumors found to have a normal chromosome complement, 4 were induced by x-irradiation.

tion and the remaining 9 by the chemical carcinogens. All 15 virus-induced tumors analyzed had a modal chromosome number of 41. (26 refs)

- 79-1704 Sarcoma Arising in Oligodendroglioma of the Brain: A Case with Intramedullary and Subarachnoid Spinal Metastases.** (Eng) Pasquier, B. (Dept. Pathology, CHU de Grenoble, B.P. 217 X 38043, Grenoble Cedex, France); Couderc, P.; Pasquier, D.; Panh, M. H.; N'Golet, A. *Cancer* 42(6): 2753-2758; 1978.

The case of a 39-yr-old man with a sarcoma arising in a left temporal oligodendroglioma is presented. Postoperatively, the patient became paraplegic because of subarachnoid metastases. The results of myelography and surgical findings strongly suggested that this metastasis was associated with an intramedullary localization. Histologically, the sarcomatous component of the tumor was both fibrosarcomatous and angiosarcomatous. The patient died following a recurrence of the cerebral tumor. The histological findings support previously reported hypotheses that sarcoma develops from the neoplastic transformation of vascular wall elements or is of endothelial origin. (25 refs)

- 79-1705 Ultrastructure of Malignant Schwannomas (Meeting Abstract).** (Eng) Chiu, H. F. (Dept. Pathology, Victoria Hosp., London, Ontario, Canada N6A 4G5); Troster, M. *Lab Invest* 40(2): 246; 1979. (no refs)

- 79-1706 Cardiac Myxoma: Biochemical Analyses and Evidence for Its Neoplastic Nature.** (Eng) Bashy, R. I. (Dept. Medicine--Rheumatology, Sch. Medicine, Univ. Pennsylvania, 536 Johnson Pavilion, 36th and Hamilton Walk, Philadelphia, PA, 19104); Nochumson, S. *NY State J Med* 79(1): 29-32; 1979.

Biochemical characterization of the ground substance from two cardiac myxomas revealed that both lesions contained approx 3 mg of hexosamine-containing macromolecules per 100 mg dry fat-free tissue, out of which about 66% was glycosaminoglycans. The absence of dermatan sulfate and the high proportion (>75% of total glycosaminoglycans) of chondroitin 4 and/or 6 sulfates suggest that cardiac myxomas are neoplastic in nature. (18 refs)

- 79-1707 Pulmonary Hypertension Caused by Neoplastic Thrombosis of the Pulmonary Artery.** (Fre) Beaufils, P. (Hopital Lariboisiere, 2 rue Ambroise-Pare, 75475 Paris Cedex 10, France); Cywiner-Golenz, C.; Perault, M. A.; Rymer, R.; Slama, R. *Arch Mal Coeur* 71(7): 816-822; 1978.

Neoplastic thrombosis of the pulmonary artery is a rare cause of pulmonary hypertension that can only be distinguished at autopsy from subacute cor pulmonale due to embolism. Two

cases are reported, one in a 51-yr-old man and one in a 41-yr-old woman, and the principal clinical and pathological characteristics are reviewed. The man entered the hospital with cyanosis, dyspnea, and an unproductive cough. Pulmonary auscultation was normal. The liver was enlarged with hepatojugular reflux. Angiography revealed dilation of the main pulmonary artery and two branches and narrowing or obliteration of the pulmonary arterioles. A right ventricular surcharge was observed on the electrocardiogram (EKG). The patient died within a month, and autopsy revealed neoplastic thrombosis of the distal arterioles of the lung. Diagnosis was carcinomatous lymphangitis with secondary invasion of arterioles. The woman was hospitalized with dyspnea, edema of the lower limbs, and cardiac irregularities. X-rays of the thorax showed a slightly enlarged heart and normal pulmonary arteries. A right branch block was noted on the EKG. Angiography confirmed massive thrombosis with obliteration of the left pulmonary field. The patient died shortly after hospitalization. Histological examination of the lung at autopsy revealed numerous white emboli obstructing the lung arterioles and a large fibrinous thrombus obstructing almost the entire right ventricular cavity. The cells composing the emboli were typical of a choriocarcinoma; however, the primary tumor was not found. (6 refs)

- 79-1708 Combined Cytological-Histological Examination of Bone Marrow. Experience with 200 Patients.** (Fre) Delacretaz, F. (Institut de pathologie, CHUV, CH-1011 Lausanne, Switzerland); Schmidt, P. M. *Schweiz Med Wochenschr* 109(1): 13-18; 1979.

The combination of bone marrow aspiration and bone marrow biopsy was evaluated in 200 patients with malignant lymphoma (53), multiple myeloma (49), myeloproliferative syndromes (35), metastases (15), and other hematological disorders (cytopenia, anemia, leukemia: 48). In 152 of the patients, the two methods were equivalent. Nevertheless, a comparison of the cytological and histological techniques provided greater diagnostic confidence. In 24 patients, the bone marrow biopsy was the only diagnostic procedure used. Bone marrow aspiration proved superior in the remaining 24 patients, as it was better able to detect small and discrete malignant infiltrates and it gave a more detailed analysis of blasts and cytological changes in cell maturation. On the basis of the results with this series of 200 patients, it is concluded that a combination of the two methods appears indispensable for evaluating lympho- and myeloproliferative syndromes, cytopenias with or without fever of unknown origin, and metastatic disease. (29 refs)

- 79-1709 Chondrosarcoma of the Hand.** (Eng) Trias, A. (Dept. Orthopaedic Surgery, Univ. Sherbrooke Sch. Medicine, Sherbrooke, Quebec, Canada); Basora, J.; Sanchez, G.; Madarnas, P. *Clin Orthop* (134): 297-301; 1978.

A case of chondrosarcoma of the hand that recurred four times over a period of 32 yr is presented. The patient was first

seen, at the age of 37, with an enchondroma of the second metacarpal; this was curetted and bone grafted. Chondrosarcoma at the site was first diagnosed 9 yr later, the time of the first recurrence. The involved finger was amputated, but the tumor recurred three additional times on the third metacarpal. Tumor spread eventually resulted in amputation at the wrist. The lesion may have been a chondrosarcoma in the beginning, or malignant transformation of benign cartilaginous seedlings left during the first surgery may have occurred. (16 refs)

- 79-1710 Chondrosarcoma of the Talus. A Case Report.** (Eng) DeBenedetti, M. J. (Dept. Orthopaedic Surgery, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016); Waugh, T. R.; Evanski, P. M.; Jordan, I.; Krijger, M. *Clin Orthop* (136): 234-237; 1978.

The unusual case of a 27-yr-old man who developed chondrosarcoma of the talus following ankle trauma is presented. The condition was misdiagnosed as ankle sprain or Sudek's atrophy by seven physicians. The correct histological diagnosis was made after radiographs showed a large soft tissue mass, soft tissue calcification, and progressive destruction of the posterior aspect of the talus. (16 refs)

- 79-1711 A Sixth Complementation Group in Xeroderma Pigmentosum.** (Eng) Arase, S. (Dept. Dermatology, Tokushima Univ. Sch. Medicine, Tokushima 770, Japan); Kozuka, T.; Tanaka, K.; Ikenaga, M.; Takebe, H. *Mutat Res* 59(1): 143-146; 1979.

A sixth complementation group was discovered in the fibroblast cells of a 45-yr-old woman with a mild case of xeroderma pigmentosum. These cells showed only 10% of the normal level of unscheduled DNA synthesis at 30 joules/m² of UV exposure. However, there was an intermediate level of DNA repair. (7 refs)

- 79-1712 Fibrous Epulis: Experience in Clinical Presentation and Treatment of 39 Cases.** (Eng) Ajagbe, H. A. (Dept. Dentistry, Univ. Coll. Hosp., Ibadan, Nigeria); Daramola, J. O. *J Natl Med Assoc* 70(5): 317-319; 1978.

The clinical features of 39 cases of fibrous epulis that occurred over a 5-yr-period are described. Thirty patients were women, 20 of whom were 21-40 yr old. Eleven were pregnant at presentation. Many epulides attained giant sizes before patients sought treatment, and they interfered with speech or mastication. In a few cases, giant cells were scattered in the lesions. No malignant cells were found in any cases. The tumor recurred in only 2/38 patients in whom the lesion was excised. A few large or recurrent fibrous epulides were mistaken for malignant lesions. (6 refs)

- 79-1713 Neurosecretory Granules in an Intrapulmonary Chemodectoma Associated with Chemodectoma-like Nodules and Multiple Arteriovenous Fistulae (Meeting Abstract).** (Eng) Spain, D. M. (Brookdale Hosp. and Medical Center, Brooklyn, NY, 11212); Chan, D. *Fed Proc* 38(3, part 2): 1155; 1979. (no refs)

- 79-1714 Cytokinetics and Vascularization of Induced Lung Metastases in C3H/He Mice.** (Eng) Gunduz, N. N. (Univ. Pittsburgh, Pittsburgh, PA). *Diss Abstr Int B* 39(8): 3643; 1979. (no refs)

- 79-1715 Lung Colony Formation: A Selective Cloning Process for Lung-Colony-Forming Ability.** (Eng) Suzuki, N. (Section Experimental Radiotherapy, Univ. Texas System Cancer Center, M. D. Anderson Hosp. Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030); Withers, H. R. *Br J Cancer* 39(2): 196-199; 1979.

The lung-colony-forming efficiency (LCFE) of cells cultured from secondary lung nodules (LC1) of mice was compared with that of cells cultured from sc mouse tumors (T1) and from the original mouse fibrosarcoma cells (FSA 1233). Single cell suspensions of 10⁴-10⁵ cells in 0.5 ml of medium were injected into tail veins of unirradiated C3Hf/Bu mice. LC1 cells had a higher LCFE than the original FSA 1233 cells, whereas the T1 cells showed an LCFE similar to that of the original FSA 1233 cells. In additional experiments using other inoculation routes, there was no difference in survival time of mice inoculated sc with lung nodule cells and those inoculated sc with FSA 1233 cells, despite the 10-fold greater artificial LCFE of the former. The data showed that the selection of increased metastatic efficiency was specific to the organ in which the metastases were passaged. (19 refs)

- 79-1716 Adenocarcinoma of the Lung: Pericardial Tamponade as the Major Presenting Feature.** (Eng) Damuth, T. E. (Dept. Medicine-Chest, Univ. Michigan Coll. Medicine, Ann Arbor, MI); Bush, C. A.; Leier, C. V. *Ohio State Med J* 75(1): 25-27; 1979.

The cases of three patients with bronchogenic adenocarcinoma presenting as pericardial tamponade are reported, and two previously reported cases are reviewed. None of the five patients manifested symptoms usually associated with primary pulmonary malignancy. No discrete mass lesions were revealed on the initial chest roentgenograms. Pericardial biopsy and pericardial and pleural fluid cytologic studies gave a high diagnostic yield. (6 refs)

- 79-1717 Fiber Endoscopy and Radiology for Gastric Ulcer, Gastric Carcinoma, and Hiatal Hernia.** (Ger) Killer-Walser, R. (Medizinische Klinik, Stadtspital Triemli, CH-8063, Zurich, Switzerland); Hess, H.; Wursch,

T. G.; Stuby, K.; Sonnenberg, A.; Bruhlmann, W.; Blum, A. L. *Schweiz Med Wochenschr* 109(1): 3-6; 1979.

Between 1973 and 1976, 306 patients underwent both fiber endoscopy and radiology examination within a 7 day period. Radiology was performed before endoscopy in 196 patients and after endoscopy in 110 patients. Follow-up studies were made of patients with histologically unproved divergent findings. In the diagnosis of gastric ulcer and gastric cancer, endoscopy with biopsy was more accurate than radiology. In the diagnosis of hiatal hernia, radiology was more accurate. Significant additional findings that were difficult or impossible to observe with endoscopy were revealed in 36% of the radiological examinations. These secondary findings included pathological gastroesophageal reflux in 55 patients, pathological tertiary esophageal contractions in 30, gastric retention in 22, carcinoma of the head of the pancreas in 4, cholelithiasis in 4, cholecystoduodenal fistula in 2, and splenomegaly in 1. Thus, endoscopy should be performed first when gastric ulcers or carcinoma is suspected. Radiology should be performed first in patients with uncharacteristic epigastric symptoms. (13 refs)

79-1718 Necessity of Gastroscopy in the Immediate Follow-up of Sutured Perforated Gastric Ulcer.

(Fre) Claudel, S. (Centre d'Endoscopie Digestive, Hôpital Edouard-Herriot, place d'Arsonval, F 69374 Lyon Cedex 2, France); Lambert, R.; Moulinier, B.; Gruffaz, B. J. *Nouv Presse Med* 7(46): 4234; 1978.

Three patients underwent surgery for perforated gastric ulcer without preceding gastroscopy or biopsy. Gastric cancer was diagnosed by intraoperative biopsy in one patient and by gastroscopy because of recurrent pains several years' postsurgery in the others. (4 refs)

79-1719 Carcinoma of the Small Intestine in Regional Enteritis. Presentation of a Case and Review of the Literature. (Eng) Floch, H. F. (Dept. Surgery, New York Univ. Coll. Medicine, New York, NY); Slaterry, L. R.; Hazzi, C. G. *Am J Gastroenterol* 70(5): 520-527; 1978.

The case of a 53-yr-old man with a 32-yr history of Crohn's disease (regional enteritis) who developed jejunal carcinoma is presented. Forty-seven previously reported small bowel carcinomas in Crohn's disease patients are reviewed. Incidence statistics and pathological features of the Crohn's carcinomas and de novo small bowel carcinomas are compared. (45 refs)

79-1720 In Vivo and In Vitro Studies of the Metastatic Process (Meeting Abstract). (Eng) Dollbaum, C. M. (Univ. California, Berkeley, CA). *Diss Abstr Int B* 39(8): 3695; 1979. (no refs)

79-1721 Precancerous Lesions of the Colon and Rectum. (Eng) Gotoh, A. (First Dept. Surgery, Gifu Univ. Medical Sch., Gifu City, Japan); Iwashima, Y. *Jpn J Surg* 8(4): 315-325; 1978.

The relationship between adenomatous polyps and the development of cancer of the colon and rectum was investigated in 46 cases of polyps and polypoid lesions of the colon and rectum operated at a Japanese hospital over the last 16 yr. The lesions were classified into three groups: adenomatous and malignant polyps (30 cases), villous tumor (1), polypoid cancer (15). In addition, the polyps were classified into five groups according to their degree of atypia. Adenomatous polyps tended to become malignant. It appeared that the larger the polyp size, the greater the incidence of severe atypia and the greater the malignant potential. Malignant polyps developed more frequently in the distal colon and rectum than in other parts. Focal and invasive cancers limited to the submucosal layer were found exclusively in the sigmoid colon and rectum. (10 refs)

79-1722 Atypical Appendiceal Carcinoid. (Eng) Stillman, R. M. (Dept. Surgery, State Univ. New York Downstate Medical Center, 450 Clarkson Ave., Brooklyn, NY, 11203); Alfonso, A.; Nicastrì, A.; Gardner, B. *NY State J Med* 79(1): 98-100; 1979.

An unusual case of appendiceal carcinoid is reported. The patient, a 27-yr-old woman, presented with right lower quadrant pain and an abdominal mass. At laparotomy, an indurated mass extending into the cecum and terminal ileum was palpated at the base of the inflamed, distended appendix. The proximal location and cecal extension of the lesion prevented simple appendectomy, and segmental resection was performed. The tumor obstructed the appendiceal lumen, extended through the muscularis into the serosal fat, and was metastatic to one adjacent lymph node. (no refs)

79-1723 The Induction of Cystitis and the Implantation of Tumours in Rat and Rabbit Bladders. (Eng) Edwards, L. (Dept. Urology, Westminster Hosp., Horseferry Road, London SW1, England); Rosin, D.; Leaper, D.; Swedan, M.; Trott, P.; Vertido, R. *Br J Urol* 50(7): 502-504; 1978.

Cystitis was induced and tumors implanted in the bladders of female Sprague-Dawley rats and female New Zealand White rabbits. The animals were anesthetized and their bladders emptied and then filled with the chemical irritant Cetavlon (CTV). CTV was left in the bladder for 30 min. Four animals of each species were sacrificed at this stage (acute experiments). In the remaining animals (6 rabbits, 10 rats), CTV was withdrawn and the bladder was filled with a suspension of Walker sarcoma (rats) or Vx2 sarcoma (rabbits). Animals were allowed to recover and then sacrificed at 7 days. In acute experiments, the normal transitional cell lining of the bladder underwent considerable change in all animals. The epithelium was hyperemic and often lifted away from the

submucosa by edema fluid. There was patchy detachment of clumps of cells, leaving the submucosal layer bare, and considerable submucosal vascular congestion and hemorrhage. In the implantation experiments, all three surviving rabbits and six surviving rats had bladder tumors. In the former, the plaques were small and mainly subepithelial; in the latter, the size of the tumor varied from small plaques to a mass almost filling the bladder. Tumor was also found in one of both kidneys in 3/6 rats. The results show that it is relatively simple to produce tumor growth in animal bladders, but only if cystitis has been induced with an irritant chemical. At the same time, if reflux occurs, it is also possible to induce tumor growth in the kidney. CTV, which is occasionally used as an antiseptic for bladder irrigations, rapidly induced a severe cystitis. The presence of infections, chemical or bacterial, may be significant in patients with recurrent bladder tumor. (4 refs)

- 79-1724 Comparative Electron-Microscopic Studies of Benign Hepatoma and Icterus in Patients on Oral Contraceptives.** (Eng) Balazs, M. (Dept. Pathology, Janos Hosp. Budapest Council, Diosarok ut 1, 1125 Budapest, Hungary). *Virchows Arch [Pathol Anat]* 381(1): 97-109; 1978.

The ultrastructure of six benign liver tumors (1 liver cell adenoma and 5 cases of focal nodular hyperplasias) and three specimens of icteric liver tissue, all from women on oral contraceptives, was compared. Most of the changes were identical in both the tumor and icteric cases. The lumen of the bile canaliculi was usually dilated by an accumulation of a filamentous substance, and the microvilli in the canaliculi were destroyed. The mitochondria, which varied greatly in size and shape, contained a large number of paracrystalline inclusions; in some cases, the external double membrane was missing. On the sinusoidal cell surface, edema of the microvilli and herniation of the cytoplasm were observed. There was an accumulation of a granular, filamentous substance in Disse's space. In some places, the plasma membrane was missing. The sinusoidal endothelial cells were hyperplastic, with increased protein production. Formation of a basement membrane was seen all around the endothelial cells. The only important difference detected between the tumor and icteric liver tissue was the formation of continuous capillaries at the site of the sinusoids in the tumor tissue. (40 refs)

- 79-1725 Liver Ultrasonography in Multinodular Hemangioendothelioma (Case Report).** (Ger) Frank, T. (Klinik für Nuklearmedizin und Radiotherapie, Stadtspital Triemli, Birmensdorfer Strasse 497, CH-8063 Zurich, Switzerland); Rampini, S. *ROEFO* 129(6): 791-793; 1978.

Liver sonography was decisive in the diagnosis of multinodular hemangioendotheliomas in a 3.5-mo-old boy. After prednisone treatment, a repeat sonography at age 13 mo showed marked regression of the tumor. The use of liver sonography

in diagnosing hemangioendotheliomas has not been reported previously. (5 refs)

- 79-1726 Differences in Cell Surface Antigens of Tumor Metastases and Those of the Local Tumor.** (Eng) Fogel, M. (Dept. Cell Biology, Weizmann Inst. Science, Rehovot, Israel); Gorelik, E.; Segal, S.; Feldman, M. *J Natl Cancer Inst* 62(3): 585-588; 1979.

Tests were made to determine whether cell surface tumor antigens of metastases differed from those of the local tumor. C57BL/6 mouse spleen lymphocytes sensitized against monolayers of a local growth of 3LL Lewis lung carcinoma (L-3LL) in the presence of syngeneic serum generated lymphocytes that were cytotoxic to L-3LL but significantly less cytotoxic to target cells derived from lung metastases (M-3LL). Lymphocytes sensitized against M-3LL were significantly more cytotoxic against M-3LL than against L-3LL cells. Anti-M-3LL cytotoxic lymphocytes, but not anti-L-3LL lymphocytes, admixed with either L-3LL cells or M-3LL tumor cells reduced lung metastasis significantly when injected into syngeneic recipients. The results indicate that cells with high metastatic capacity and distinct antigenic properties exist within the tumor cell population and that immunoselection might be involved in the production of lung metastases. (16 refs)

- 79-1727 The Role of Genetic Factors in the Etiology of Wilms' Tumor. Two Pairs of Monozygous Twins with Congenital Abnormalities (Aniridia; Hemihypertrophy) and Discordance for Wilms' Tumor.** (Eng) Maurer, H. S. (Dept. Pediatrics, Northwestern Univ. Medical Sch., Children's Memorial Hosp., 2300 Children's Plaza, Chicago, IL, 60614); Pendergrass, T. W.; Borges, W.; Honig, G. R. *Cancer* 43(1): 205-208; 1979.

Wilms' tumor was diagnosed in two children, each with an identical twin. In one of the pairs the aniridia syndrome with psychomotor retardation was present in both children, but Wilms' tumor was found in only one. In the other pair hemihypertrophy as well as Wilms' tumor were identified in one child, but neither of these abnormalities was present in her twin sister. These findings support the hypothesis that the development of Wilms' tumor requires the occurrence of two successive mutational events, one of which may be a germinal mutation. The presence of aniridia, hemihypertrophy, or other associated congenital abnormalities may aid in distinguishing between hereditary and sporadic forms of Wilms' tumor. (21 refs)

- 79-1728 Intrarenal Neuroblastoma Mimicking Wilms' Tumor.** (Eng) Shende, A. (Div. Pediatric Hematology-Oncology, Long Island Jewish-Hillside Medical Center, New Hyde Park, NY); Wind, E. S.; Lanzkowsky, P. *NY State J Med* 79(1): 93; 1979.

The case of a 13-mo-old boy with neuroblastoma arising in an intrarenal location and presenting the classic radiographic features of Wilms' tumor is reported. (2 refs)

- 79-1729 Carcinoid Tumor of the Kidney. Report of a Case.** (Fre) Lanson, Y. (Service d'Urologie, C.H.U. Bretonneau, 37000 Tours, France); Bruant, D.; Benatre, A.; Rivalan, P.; Brizon, J. *J Urol Nephrol (Paris)* 84(1/2): 47-51; 1978.

A carcinoid tumor of the kidney was diagnosed in a 65-yr-old man who entered the hospital with a fever that had persisted for several weeks, despite antibiotic therapy. A large, painful mass palpated in the lumbar region and an *Escherichia coli* pyuria led to the diagnosis of pyonephrosis of a horseshoe kidney. At surgery, pyonephrosis and stenosis of the renal calix junction were observed, and the right half of the horseshoe kidney was excised. A carcinoid tumor 2 cm in diameter was found upon histological examination of the specimen. Dysgenetic cellular elements were observed in the region of the tumor. Complete evaluation of the patient failed to reveal a tumor at any other site. It was concluded that the kidney carcinoid tumor resulted from a neoplastic change in a dysplastic zone of the kidney. Carcinoid tumors of the kidney support the hypothesis that the renal blastema is derived not only from the mesenchyme but also from the neural crests, since cells from the crest have the potential of differentiating into cells of the diffuse endocrine system. (43 refs)

- 79-1730 Urothelial Tumors in Essential Fatty Acid Deficient Rats (Meeting Abstract).** (Eng) Monis, B. (Instituto de Biologia Celular, Universidad Nacional de Cordoba, Casilla Postal 220, 5.000 Cordoba, Argentina); Eynard, A. R. *Fed Proc* 38(3, part 2): 1451; 1979. (no refs)

- 79-1731 The Appearance of Tumor Cells in the Milk of C3H Mice in Successive Pregnancies (Meeting Abstract).** (Eng) Miller-Catchpole, R. (Dept. of Pathology, Univ. Illinois at the Medical Center, Chicago, IL); McGrew, E. A.; Catchpole, H. R. *Anat Rec* 193(3): 625; 1979. (no refs)

- 79-1732 Isolated Adenocarcinomatous Transformation in Uterine Adenomyosis.** (Fre) Baril, A. (Service d'Anatomie Pathologique, CHU Bellevue, boulevard Pasteur, 42023 Saint-Etienne Cedex, France); Boucheron, S.; la Selve, A. *Arch Anat Cytol Pathol (Paris)* 26(3/4): 177-180; 1978.

Adenomyoma was tentatively diagnosed in a 48-yr-old nullipara who initially refused to undergo surgery. Consent was given 4 yr later, and subtotal hysterectomy with adnexectomy was performed. Histological examination of the resected tissues revealed polyfibromyomatosis with subserous and interstitial myomas. The fibromyomas were infiltrated by an en-

dometrial adenocarcinoma. Several foci of adenomyosis were seen in the uterine wall. (31 refs)

- 79-1733 Behavior of Cervical Epithelium During Carcinogenesis: Autoradiography of Tritiated Cytidine in the C57BL Mouse.** (Eng) Rubio, C. A. (Inst. Pathology, Karolinska Sjukhuset, S-104 01 Stockholm 60, Sweden). *J Natl Cancer Inst* 62(3): 629-631; 1979.

An investigation was made of the autoradiographic patterns of the cervical epithelia of 39 virgin C57BL mice after in vivo injection of ³H-cytidine. Of the 22 animals whose cervixes were painted 2x/wk with 1% benzo(a)pyrene soln for 5 mo, 8 developed intraepithelial atypias and 2 had invasive carcinoma. The mean number of silver grains in individual cells increased from histologically normal cervical epithelium through atypical epithelium to invasive carcinoma. The autoradiographic patterns in normal, atypical, and invasive carcinoma cells apparently reflected quantitative differences in normal, atypical, cytidine incorporation. These differences may denote an increased demand for RNA precursors in the cervical epithelium during carcinogenesis. (9 refs)

- 79-1734 Extramammary Paget's Disease.** (Eng) Breen, J. L. (St. Barnabas Medical Center, Livingston, NJ); Smith, C. I.; Gregori, C. A. *Clin Obstet Gynecol* 21(4): 1107-1115; 1978.

A histopathologic and clinical evaluation of 13 patients with vulvar Paget's disease seen during 1970-1977 is presented, and reports on the disease published in the past 20 yr are reviewed. Vulvar Paget's disease is a rare disease of postmenopausal women primarily in the sixth and seventh decades, and it involves the skin and its appendages in a multifocal fashion. It is commonly manifested by vulvar pruritus, irritation, or a burning sensation, and it usually appears as a well-defined, moist, reddish lesion involving the labia and occasionally extending over the entire vulva and peritoneum. It is present as an in situ lesion for a long time before it invades the dermis. Five of the 13 patients and 25/85 from the literature had an associated or prior malignancy. Including 7 patients with breast cancer, a total of 16 of these malignancies were related to the genital tract. Although the recurrence rates were similar at different levels of histologic involvement, the death rates of 0% and 8.3% with epidermal and glandular involvement, respectively, increased to 50% when invasion of the dermis was present. Theories for the origin of this disease fall into three basic categories: (1) origin from an underlying ductal or glandular carcinoma; (2) an intraepithelial origin with subsequent sweat gland and dermal involvement; and (3) a multifocal origin. (21 refs)

- 79-1735 Diseases of the Vulva Presenting as White Lesions.** (Eng) Young, A. W. (St. Luke's Hosp. Center, New York, NY); Tovell, H. M. *Clin Obstet Gynecol* 21(4): 1023-1039; 1978.

The various diagnoses of white lesions of the vulva and their incidence in 484 patients who attended a cutaneous-vulva clinic during 1971-1977 are reported. The 14 different conditions diagnosed were divided into two clinically distinguishable groups: (1) those in which leukoderma was invariably present and persisted throughout the course of the disease; and (2) those in which leukoderma was a complicating feature of an active or resolving inflammatory process or became apparent as a result of increased moisture superimposed on hyperkeratosis. The first group included 77 cases of vulvar dystrophy [lichen sclerosus (68), hyperplastic dystrophy (4), lichen planus (1), and mixed dystrophy (4)] and 22 cases of vitiligo. The second group included scar (2), candidiasis (148), lichen simplex chronicus (81), intertrigo (29), psoriasis (12), condyloma latum (4), verruca genitalis (88), intraepithelial neoplasms (7), and postinflammation lesions (14). None of the 77 vulvar dystrophy patients evidenced neoplasia during the observation period. The carcinoma in situ seen in seven patients frequently showed whiteness because of hydration of the dyskeratotic horny layer. It is concluded that only an extremely small percentage of patients in the population served by the clinic who presented with a white or potentially white lesion of the vulva had an active neoplastic or preneoplastic process. (17 refs)

- 79-1736 Classification of Vulvar Diseases.** (Eng) Tovell, H. M. (St. Luke's Hosp. Center, New York, NY); Young, A. W. *Clin Obstet Gynecol* 21(4): 955-961; 1978.

The operation of a cutaneous-vulvar clinic is described, and a simple classification of vulvar diseases and the frequency with which they were encountered at the clinic are presented. In the first 1,000 consecutive patients, there were 64 different diagnoses. Each condition was classified according to its point of origin into one of three groups: cutaneous-vulvar disorders (CVD, 78%), vulvovaginal disorders (19.4%), and undetermined disorders (2.6%). Neoplasms, including seven carcinomas in situ and four invasive carcinomas, were diagnosed in 198/703 patients with primary CVD. (3 refs)

- 79-1737 Mixed Mesodermal Tumor and Clear Cell Carcinoma Arising in Ovarian Endometriosis.** (Eng) Cooper, P. (Pathology Dept., Level 5, Addenbrooke's Hosp., Hills Road, Cambridge, England). *Cancer* 42(6): 2827-2831; 1978.

A case of clear cell carcinoma and mixed mesodermal tumor arising together in a focus of ovarian endometriosis is presented. The patient, a 53-yr-old woman who was 3 yr postmenopausal, underwent surgery for the removal of a right ovarian cyst. The endometrial cyst contained papillary nodules showing features of clear cell carcinoma. The surface of the largest papillary nodule had a clear cell pattern, but the stroma beneath contained abundant striated muscle. Strap-shaped rhabdomyoblasts were present, and a single

focus of well-formed cartilage was identified in the midst of striated muscle. The epithelial component of the mesodermal tumor consisted of clear cells. The origin of this tumor from within a focus of endometriosis supports the theory that both the epithelial and mesodermal components are of müllerian (paramesonephric) origin. (20 refs)

- 79-1738 Familial Occurrence of Testicular Neoplasms (in Cousins).** (Eng) Madduri, S. D. (Dept. Surgery, New Jersey Medical Sch., Newark, NJ); Gellman, A. C.; Sporer, A.; Seebode, J. J. *Urology* 13(1): 67-69; 1979.

The occurrence of testicular neoplasms in two families is reported. In the first family, two brothers and their second cousin (maternal uncle's daughter's son) were affected, and in the second family, two first cousins were affected. Eighteen reports of a familial occurrence of testicular tumors have appeared in the literature, but this is the first report of these neoplasms occurring in cousins. The occasional familial incidence of the disease, its relative rarity in blacks, and its association with cryptorchism are consistent with a genetic influence, but such an influence has not been established. It is suggested that the other members of the family be checked when a testicular tumor is detected. (21 refs)

See also:

- *(Rev.): 79-1207, 79-1212, 79-1229, 79-1238, 79-1248, 79-1255, 79-1257, 79-1263, 79-1264, 79-1265, 79-1266, 79-1267, 79-1268, 79-1269, 79-1270, 79-1271, 79-1272, 79-1273, 79-1277, 79-1278, 79-1279, 79-1280, 79-1281, 79-1285, 79-1296, 79-1298, 79-1299, 79-1302.
 *(Chem.): 79-1311, 79-1312, 79-1322, 79-1323, 79-1329, 79-1332, 79-1346, 79-1356, 79-1366, 79-1367, 79-1368, 79-1370, 79-1379, 79-1385, 79-1386, 79-1391, 79-1393, 79-1402, 79-1405, 79-1413, 79-1430, 79-1475, 79-1484, 79-1489.
 *(Phys.): 79-1495, 79-1503, 79-1508, 79-1518, 79-1521, 79-1522, 79-1525, 79-1526, 79-1527, 79-1528, 79-1531.
 *(Viral): 79-1549, 79-1558, 79-1580, 79-1598, 79-1611, 79-1613, 79-1628, 79-1650, 79-1651.
 *(Immun.): 79-1657, 79-1659, 79-1677, 79-1679, 79-1683, 79-1686, 79-1687.
 *(Epid.-Biom.): 79-1740, 79-1754, 79-1767.

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- 79-1739 Mortality Experience of Arsenic-exposed Workers.** (Eng) Pinto, S. S. (ASARCO, Inc., Takoma, WA); Henderson, V.; Enterline, P. E. *Arch Environ Health* 33(6): 325-331; 1978.

The mortality experience of 527 pensioners from a copper smelter who were aged 65 or over between 1949 and 1973 was studied. The av duration of employment was 28 yr, and it ranged from 7 to 54 yr. An index of arsenic exposure was developed for all operations in the plant for 1973. This was applied to all individuals studied, so that a comparative measure could be made of each individual's working-life exposure to arsenic. The overall mortality of this cohort was 12.2% higher than that for men living in the same area, of the same ages, and in the same time periods. The excess mortality was due chiefly to respiratory cancer, for which mortality was three times that expected. This excess was not due to cigarette smoking. Because other contaminants were present in the atmosphere, it is not certain that arsenic was entirely responsible for the respiratory cancer observed, yet a close association with arsenic seems highly likely. (15 refs)

- 79-1740 Study of 201 Workers in an Asbestos Textile Factory.** (Fre) Molina, C (Clinique de Pneumologie, Hopital Sabourin, B.P. 12, La Plaine, 63018 Clermont-Ferrand, France); Cheminat, J. C.; Tourreau, A.; Brun, J.; Maillet, J.; Petit, R.; Gourgand, A. J. *Rev Fr Mal Respir* 6(5): 471-482; 1978.

Among 201 employees in an asbestos textile factory, 34% had x-ray evidence of parenchymal and pleural disorders. Eighty-nine workers had decreased pulmonary function and 25 had decreased overall CO diffusion. There were three cases of cancer (in the lungs, larynx, and stomach, respectively). Correspondence analysis and Fischer's discriminating analysis demonstrated that there was a positive correlation between the degree of pulmonary insufficiency and the amount of dust to which the workers were exposed. At the end of the study, 149 workers were considered to be free of pulmonary disease and 20 were diagnosed with asbestosis. The remaining 32 workers demonstrated either an isolated disorder upon functional examination (including the 3 cancer cases) or asbestos particles in the sputum and were considered a high-risk group, to be kept under strict surveillance. (26 refs)

- 79-1741 Radiation Therapy of the Nasopharynx: A 30 Year View.** (Eng) Loeb, W. J. (2065 Adelbert Road, Cleveland, OH, 44106). *Laryngoscope* 89(1): 16-21; 1979.

The results of a 15- to 30-yr follow-up study of radium therapy to the nasopharynx for serous otitis, Eustachian tube ob-

struction, and conductive deafness are reported, and the relevant literature is reviewed. In the follow-up study, 28/41 patients who had Ra treatment between 1946 and 1961, when it was discontinued, were reexamined in 1976-1977. No tumor or other complication was found. Twenty-four had good results from treatment. The literature cases include about 25,000 treatments reported by the originator of the method, one review of a 27-yr experience, and series of 263, 552, 480, and 2,400 patients. No malignancies were reported in any of these series 15-30 yr after therapy. It is suggested that Ra treatment using the Crowe applicator is still a useful treatment of persistent recalcitrant serous otitis with hearing loss and that it should not have been abandoned because of public pressure and fear of radiation-induced cancer. (26 refs)

- 79-1742 Malignant Melanomas in New Mexico: A Model for One Kind of Environmental Pathology Study (Meeting Abstract).** (Eng) Key, C. R. (Univ. New Mexico Sch. Medicine, Albuquerque, NM, 87131); Black, W. C. *Fed Proc* 38(3, part 2): 1353; 1979. (no refs)

- 79-1743 Radiation Exposures of Hanford Workers: A Critique of the Mancuso, Stewart and Kneale Report.** (Eng) Anderson, T. W. (Dept. Preventive Medicine and Biostatistics, Faculty Medicine, Univ. Toronto, Ontario, Canada). *Health Phys* 35(6): 743-750; 1978.

A published analysis of Hanford (Washington) nuclear plant mortality data based mainly on a case/control comparison of mean cumulative radiation records in cancer vs noncancer deaths of Hanford employees is critically reviewed. The analysis indicated the occurrence of approx 25 radiation-induced cancers, mainly cancers of the reticuloendothelial system (RES), especially myeloid leukemia and myeloma. A second analysis, based on a proportionate mortality comparison of the Hanford deaths with general US mortality patterns, appeared to confirm this conclusion. This second analysis, however, was not carried out using age-adjusted mortality rates. In addition, both the corrected and uncorrected figures contradicted the main analysis, indicating an apparent deficit in deaths from leukemia (the cancer most likely to be increased by exposure to external ionizing radiation) as well as from total RES cancers. The main analysis was based on mean cumulative exposures that were distorted by a few abnormally high figures, leading to implausible estimates of excess deaths. The two methods, however, were consistent in indicating some excess deaths from myeloma, cancer of the pancreas, and possibly cancer of the lung, in addition to the deficit in leukemia deaths. Previous experience with ionizing radiation has not shown it to be particularly liable to induce myeloma or pancreatic cancer. An investigation of the work histories of these cases might yield some insight into another

occupational or non-occupational cause of these two diseases. (6 refs)

- 79-1744 Impact of Long-Term Filter Cigarette Usage on Lung and Larynx Cancer Risk: A Case-Control Study.** (Eng) Wynder, E. L. (Div. Epidemiology, Naylor Dana Inst. Disease Prevention, American Health Foundation, 320 E. 43d St., New York, NY, 10017); Stellman, S. D. *J Natl Cancer Inst* 62(3): 471-477; 1979.

A case-control study was conducted among 1,034 white male and female hospital patients in six US cities with histologically proved lung cancer (Kreyberg type 1, squamous and rat cell types; 684 patients) or larynx cancer (350 patients). After adjustment for duration of smoking habit, inhalation, and butt length, relative risks of developing lung or larynx cancer were consistently lower among long-term smokers of filter cigarettes than among smokers of nonfilter cigarettes, irrespective of quantity smoked. Relative risks in all groups declined with increased years of smoking cessation. The observed risk reduction among current smokers of filter cigarettes was consistent with that expected, considering that these persons had smoked the older high-tar nonfilter cigarettes for a large proportion of their lives. (35 refs)

- 79-1745 Bronchial Cancer in Hong Kong 1976-1977.** (Eng) Chan, W. C. (Dept. Pathology, Univ. Hong Kong, Queen Mary Hosp., Hong Kong); Colbourne, M. J.; Fung, S. C.; Ho, H. C. *Br J Cancer* 39(2): 182-192; 1979.

The relationship between smoking and bronchial cancer among the Chinese in Hong Kong was studied between 1976 and 1977 with the use of 208 men and 189 women with cancer and 204 male and 189 female controls. Among the cancer patients, 20% fewer men and 30% fewer women were nonsmokers and 24% more men and 20% more women were heavy or very heavy smokers compared with controls. Among the men there was no indication that type of cancer was related to the amount smoked, whereas among women there was an increased relative risk for squamous and small cell anaplastic carcinomas associated with heavy or very heavy smoking. Adenocarcinomas and large cell anaplastic carcinomas occurred more often in men <50 yr old than among older men. The occurrence of bronchial cancer among nonsmoking women (nearly half of the female patient population) could not be attributed to lying about smoking habits, misdiagnosis, age, occupation, education, marital status, age at first marriage, number of children, place of origin, place of residence, or passive exposure to tobacco smoke. More female cancer patients used kerosene or gas for cooking than did controls, but 15 nonsmoking cancer patients did not cook at all. The cause of cancer in the nonsmoking women remains unknown. (15 refs)

- 79-1746 Pleural Plaques in a Health Survey Material: Frequency, Development and Exposure to Asbestos.** (Eng) Hillerdal, G. (Dept. Lung Medicine, Univ. Hosp., S-750 14 Uppsala, Sweden). *Scand J Respir Dis* 59(5): 257-263; 1978.

Mass x-ray screening of residents in Uppsala County (population 230,000), was undertaken in order to detect individuals with hyaline pleural plaques (PP). A total of 508 cases, 492 of whom were men, were found during 1970-1976. Of the 369 men in whom a history was taken, 79.4% had been exposed to asbestos (most via occupation) and 78.9% were smokers or had smoked at the time of asbestos exposure. The mean latency time from first exposure to asbestos and first x-ray evidence of PP was 32.7 yr in the 217 men for whom these data were available. PP were found almost exclusively in men over 40, with the highest frequency occurring in men in the age group 60-64 yr. Bronchial carcinoma developed in 3/492 men after the diagnosis of PP had been made. All three were heavy smokers. Pulmonary fibrosis occurred in 19 men. A history was obtained in 15/16 women, and in 8/15 there were strong reasons to suspect that the PP originated from asbestos. (21 refs)

- 79-1747 Primary Lung Cancer. A Retrospective Study.** (Nor) Rostad, H. (Kirurgisk avdeling A, Rikshospitalet, Norway); Vale, J. R. *Tidsskr Nor Laegeforen* 98(33): 1670-1673; 1978.

A series of 1,053 lung cancer patients (895 men and 158 women) treated over a 10-yr period was studied retrospectively. The incidence was highest in the age bracket 50-70 yr for both men and women. Smoking habits were not established for 29% of the women and 19% of the men. Among the remainder, 33% of the women and 76% of the men were smokers. Squamous epithelial carcinoma was diagnosed in 238 cases, undifferentiated carcinoma in 77, small cell anaplastic carcinoma in 56, adenocarcinoma in 133, carcinoid tumors in 21, and other tumors in 19; 509 cases were not classified histologically. (14 refs)

- 79-1748 The Significance of Cancerogeneous Noxes in the Formation of Pulmonary Hamartochondromas as Compared to Carcinomas and Sarcomas of the Lung.** (Ger) Gebauer, C. (Bezirkskrankenhaus für Lungenkrankheiten Zschadras, Altmarkt 14, DDR-801 Dresden, E. Germany). *Arch Geschwulstforsch* 4(48): 761-769; 1978.

The roles of carcinogens and other factors in the development of pulmonary cancer were studied in 104 cases of pulmonary hamartochondromas occurring in 1961, and in 41 cases of primary pulmonary sarcoma occurring between 1957 and 1974. All cases were seen at a single clinic in Zschadras, East Germany. Of the patients with pulmonary carcinoma, 90.6% were men, and 89.7% smoked cigarettes (76.5% were heavy smokers). Of the patients with hamartochondromas, 80% were men, and 91.4% were cigarette smokers (68.8% heavy

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smokers). Only 48.8% of the patients with pulmonary sarcoma were men, and 70% were smokers (21.4% heavy smokers). Coexistent chronic bronchitis occurred in 58.3% of patients with pulmonary carcinoma, in 45.2% of patients with hamartochondroma, and in 24% and 13.2% of patients with pulmonary adenocarcinoma and sarcoma, respectively. The percentage of men with hamartochondromas who were exposed to radiation was higher than that of men with carcinoma (33.7% vs 13%). (38 refs)

79-1749 Lung Cancer Mortality and Hydrogen Sulfide Sources in Southeastern Coastal States (Meeting Abstract). (Eng) Hitchcock, D. R. (Hitchcock Association, Farmington, CT, 06032). *Fed Proc* 38(3, part 2): 1270; 1979. (no refs)

79-1750 Opium and Oesophageal Cancer in Iran (Letter to Editor). (Eng) Hewer, T. F. (Vine House, Henbury, Bristol, England). *Lancet* 1(8106): 45; 1979.

A previous suggestion that the presence of mutagenic substances in sukhteh (prepared from scrapings of tar from opium pipes) might be a cause of esophageal cancer among Iranians who chew it is defended. The criticism was based on the belief that <5% of the cancer patients used opium. In contrast, it appears that >60% of these patients actually use the narcotic. (no refs)

79-1751 Are Patients Who Are Less Susceptible to Impairment of Pulmonary Function by Smoking More Predisposed to Development of Gastric Cancer? (Meeting Abstract). (Eng) Luk, G. D. (Dept. Medicine and Epidemiology, Johns Hopkins Univ. Sch. Medicine and Hygiene, Baltimore, MD); Meyer, M. B. *Clin Res* 26(4): 613A; 1978. (no refs)

79-1752 Correlation Between Nutrition and Mortality due to Some Chronic Degenerative Diseases. (Ger) Ulbricht, G. (Zentralinstitut für Ernährung, Akademie der Wissenschaften der DDR, Arthur-Scheunert-Allee 114/116, DDR-1505 Potsdam-Rehbrücke, E. Germany); Haenel, H.; Oehmsch, W.; Erhardt, V. *Z Gesamte Hyg* 24(12): 929-934; 1978.

Correlations between the crude standardized mortality rates for 12 diseases and nutrition were analyzed for 18 industrialized countries. Negative correlations were found between gastric cancer and the consumption of animal protein, fat, fatty acids, cholesterol, and milk. Positive correlations were found between gastric cancer and the consumption of cereal products and complex carbohydrates. The correlations were weak in the age bracket 15-35 yr, becoming more significant in middle age, and disappearing after 75 yr in both men and women. The correlations were always weaker for women than for men. Negative correlations were found between in-

testinal cancer mortality and the consumption of vegetable protein, complex carbohydrates, and cereal products. Positive correlations were seen between intestinal cancer mortality and the consumption of fat, cholesterol, sugar, meat, eggs and beer. The sex differences were negligible. Correlations were seen only in the age group >35 yr in men and >45 yr in women, and they intensified with advancing age. (8 refs)

79-1753 Gastric Carcinoma in the Dutch Province of Zeeland: An Epidemiological Study. (Dut) Bijlsma, F. (Pathologisch-Anatomisch Laboratorium, Streeklaboratorium Zeeland, Middelburg, Netherlands); Planteydt, H. T. *Ned Tijdschr Geneesk* 122(51): 2013-2020; 1978.

The incidence of gastric cancer in the Dutch province of Zeeland was studied epidemiologically using data on 392 patients recorded during 1961-1970 in a central registry in Middelburg. Striking local differences were observed, and these differences were even more apparent when mortality data for this period were compared with those for the previous years. Data on patient age, sex, and histological type of tumor did not diverge greatly from the parameters for the disease in general. (10 refs)

79-1754 Pancreas Cancer. I. Duct Adenocarcinoma. A Clinical-Pathologic Study of 380 Patients. (Eng) Cubilla, A. (No affiliation given.); Fitzgerald, P. J. *Pathol Annu* 13(1): 241-289; 1978.

A detailed clinical-pathologic study of 380 patients with duct cell adenocarcinoma, the most common type of pancreas cancer, is reported. The peak number of patients were in their 70's for both sexes, with a male/female ratio of 1:5. White patients predominated (92%), and the most prevalent religion was Jewish (42%). Sixty-eight percent of the men and 25% of the women were smokers and 24% of the men and 4% of the women were alcoholics. Of the 14 men who were simultaneously heavy smokers and excessive drinkers, three had a second primary tumor and two of these were alcohol-tobacco-associated cancers. Diabetes occurred in 119 patients and thromboembolic disease in 55. In 31% of the patients, there was a history of cancer in the immediate family. About two-thirds of the patients presented with jaundice and elevated liver enzymes. In 80% of patients, the cancer was localized to one site: head of the pancreas, 61%; body, 13%; and tail, 5%. Staging of 333 patients indicated that 14% were stage I, 21% were stage II, and 65% were stage III cases. All pancreas cancers tended toward regional intraabdominal spread when seen clinically or at exploratory operation. At autopsy metastases to the liver and lymph nodes were seen in 70%-80% of patients. Clinical presentation as metastasis in peripheral lymph nodes, skin, or bones from an inapparent primary was seen in 13% of the patients. Tumor size and stage were closely correlated in many cancers. The overall mean survival period was 4 mo, irrespective of treatment. (115 refs)

- 79-1755** Carcinoma of the Colon and Rectum in North-East Scotland. (Eng) Kyle, J. (Woodend General Hosp., Aberdeen, Scotland); Petrie, M. X. *J R Coll Surg Edinb* 24(1): 22-27; 1979.

A recent analysis revealed that Scotland, particularly the northeast region, has the highest death rate in the world for colon carcinoma and that it ranks sixth for rectal carcinoma. To obtain a true picture of these diseases in a relatively closed community, every patient with carcinoma of the colon or rectum admitted to Aberdeen hospitals during 1975 was interviewed. Only patients permanently residing in Aberdeen or in three adjacent counties were included in the series. During 1975, 202 new cases of colorectal carcinoma were diagnosed, an incidence of 51.8/100,000. There were 100 men and 102 women. None of the patients were < 30 yr old; 87 were aged 50-69, 93 were aged 70-89. The chances of a man > 50 yr old developing a tumor were much greater in all sites except the transverse colon. The concept that carcinoma of the right colon is commoner in women needs to be revised. Even younger men were more likely than women to have rectal carcinoma. The risk increased steadily at all sites with age. Only 13 patients gave a definite history of large bowel carcinoma in a first-degree relative. For men, the incidence (per 100,000) was 110.9 in the city and 93.4 in rural areas; these values women for were 96.0 and 80.2, respectively. Thus, risk of large bowel cancer was greater in city dwellers in Northeast Scotland than among rural dwellers. The latter may consume larger quantities of vegetables such as cabbage and turnips, which may speed up intestinal transit time. The benzpyrene hydroxylase in these vegetables may break down some potential carcinogens in the gut. It was hard to determine the complete occupational history of many of the men. Most of the women were housewives. Great difficulty was also experienced in recording dietary habits. (14 refs)

- 79-1756** Epidemiological Report on Rectal Cancer. (Ger) Magyar, K. (Abteilung Gesundheits- und Sozialwesen, Rat der Stadt Halle, DDR-409 Halle-Neustadt, E. Germany); Heindorf, J.; Berger, H. J. *Z Gesamte Hyg* 24(12): 944-946; 1978.

Epidemiological data on the occurrence of rectal cancer in the Halle region of East Germany during 1953-1962 are presented. The incidence, per 100,000 inhabitants, was 13.7 in 1953, and 14.7 in 1956 and 1962. Rectal cancer accounted for 4.5% of all tumors in 1953 and for 4.4% in 1962. A total of 428 cases were diagnosed: 208 in men and 220 in women. The incidence was highest in the age bracket 60-80 yr in both sexes. (11 refs)

- 79-1757** Assuring the Quality of Questionnaire Data in Epidemiologic Research. (Eng) Gordis, L. (Dept. Epidemiology, Johns Hopkins Sch. Hygiene and Public Health, 615 N. Wolfe St., Baltimore, MD, 21205). *Am J Epidemiol* 109(1): 21-24; 1979.

The quality of questionnaire or interview data in epidemiologic research is a matter of concern. Problems in eliciting valid histories are further compounded by (1) the variability in the interview or questionnaire instruments used in different studies and (2) the impossibility of assessing the comparability of these studies because of the lack of sufficient information on these instruments in published papers. Steps to improve the quality of the data are listed. (2 refs)

- 79-1758** Epidemiologic Data for Environmental Determination of Urinary System Tumours and Nephropathy in an Endemic Region. (Eng) Chernozemsky, I. N. (Inst. Oncology, Medical Acad., Sofia 1156, Bulgaria); Petkova-Bocharova, T.; Stoyanov, I. S.; Nikolov, I. G. *Arch Geschwulstforsch* 48(8): 756-760; 1978.

The familial pattern and time clustering of patients with urinary system tumors (UST; 138 patients), endemic neuropathy (EN; 714), and UST + EN (55) diagnosed in nine hyperendemic villages in the Vratza district of Bulgaria during 1965-1976 were examined. There were 144 spouses among these patients, and nearly 50% of them came from nonendemic families or villages. Among the 907 cases, 471 were blood relatives; 799 familial relationships were encountered, because some people had more than one relative: 165 persons were parents and children, 254 siblings, 215 second-degree relatives, and 165 third-degree relatives. In 21% of the 91 parent-child pairs the offsprings were diagnosed before the parent, and in 14% they were diagnosed in the same year. Among the 166 pairs of siblings, 19% were diagnosed in the same year and in 33% the younger was diagnosed first. These data indicate that the relatives under study did not reveal any familial pattern specific for an inheritance of the diseases. Their pattern followed, rather, the size of the population at greater risk; ie, persons 40-60 yr old, particularly women, indicating a decisive role for environment in the etiology of both diseases. This hypothesis is supported by data showing a closer proximity in time of onset than in age of onset of the diseases among first-degree relatives. (22 refs)

- 79-1759** Liver Oncogenesis and Steroids. (Eng) Christopherson, W. M. (Dept. Pathology, Health Sciences Center, Univ. Louisville, Sch. Medicine, Louisville, KY); Mays, E. T.; Barrows, G. H. *In: Prog Clin Cancer* 7: 153-163; 1978.

One hundred and forty-eight cases of liver tumors, most of which were associated with oral contraceptives, were reviewed with regard to relationship to steroids and type of steroid, patient age, signs and symptoms, tumor classification, gross and histopathologic findings, treatment, pathogenesis, and risk factors. Most tumors were benign, but 19 were hepatomas. The biological potential of benign liver tumors is briefly discussed. (38 refs)

- 79-1760** Hepatocellular Carcinoma, Hepatitis B and Measles (Letter to Editor). (Eng) Ree, G. H.

(Hosp. Tropical Diseases, London, England). *Br J Cancer* 39(2): 205-206; 1979.

Sixteen Africans with hepatitis B surface antigen (HBsAg)-associated primary hepatocellular carcinoma (PHC) were studied to determine whether they had measles antibody levels greater than those of normal controls and, thus, whether these levels could be used as a possible marker of previous chronic liver disease in the genesis of PHC. Four patients had no serological evidence of past measles, and measles antibody levels in the HBsAg-positive patients were no higher than those in 16 normal, HBsAg-negative controls. (7 refs)

79-1761 Hepatitis B Virus Infection in Southern African Blacks with Hepatocellular Cancer. (Eng) Kew, M. C. (Dept. Medicine, Univ. Witwatersrand Medical Sch., Hospital Hill, Johannesburg 2001, S. Africa); Desmyter, J.; Bradburne, A. F.; Macnab, G. M. *J Natl Cancer Inst* 62(3): 517-520; 1979.

Sera from 289 southern African blacks with histologically proved hepatocellular carcinoma (HCC) were tested for hepatitis B surface antigen (HBsAg) and its specific antibody, anti-HBs, in order to determine whether there is an association between hepatitis B virus (HBV) infection and HCC in these people. HBsAg was present in the sera of 61.6% of the patients compared with only 11.3% of age-matched, sex-matched, and ethnically matched controls ($2 < 0.001$). Anti-HBs was found in 17% of the patients and 41.7% of the controls ($p < 0.001$). In 74 patients studied in more detail, antibody against hepatitis B core antigen (anti-HBc) was detected in 89%, almost always in high or moderately high titer. Anti-HBc was found in 37.5% of the controls. Active HBV infection, as indicated by positive tests for HBsAg or anti-HBc, was present in 91% of the patients compared with 39.4% of the controls ($p < 0.001$). Hepatitis B envelope (e) antigen was detected in 2.3% and its specific antibody in 20.5% of the patients. The corresponding figures in the controls were 0% and 55%. HBs antigenemia was more common in younger patients with HCC. No relationship was demonstrated between α -fetoprotein and HBs antigenemia. HBV infection was equally common in patients with and without cirrhosis in the nontumorous liver. (36 refs)

79-1762 Age of Parents of Children with Nephroblastoma (Letter to Editor). (Fre) Spira, A. (IN-SERM, 16 bis, av. P.-Vaillant-Couturier, 94800 Villejuif, France); Lemerle, J.; Lazar, P. *Rev Epidemiol Sante Publique* 26(4): 361-362; 1978.

A statistical study of the age of mothers and fathers at the time of birth of children who later developed a nephroblastoma revealed no relationship. The study involved 209 children with nephroblastoma hospitalized during 1960-1970. (3 refs)

79-1763 Changing Patterns in Age Distribution of Renal Carcinoma Patients. (Eng) Noronha, R. F. (Dept. Urology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX); Johnson, D. E.; Guinee, V. F.; Borlase, B. C. *Urology* 13(1): 12-13; 1979.

The age distribution of renal carcinoma patients admitted to a Houston, Texas, hospital between 1957 and 1976 was reviewed. Of the 890 patients included in the study, 79.6% were aged 40-69 yr. There was a significantly increased representation of patients aged 40-69 yr in each 5-yr period within the 20-yr study period; there was no relative increase in the proportion of patients aged 50-59 yr or 60-69 yr. The proportion of patients aged 40-49 yr increased steadily from 1957 to 1971, but began to decrease from 1972 to 1976. (6 refs)

79-1764 Effect of Age on Incidence of Breast Cancer in Females. (Eng) Moolgavkar, S. H. (Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA, 19111); Stevens, R. G.; Lee, J. A. *J Natl Cancer Inst* 62(3): 493-501; 1979.

Incidence and mortality data on breast cancer (BC) in women from various Western and Japanese populations were compared. Incidence data were examined for Connecticut (1935-1972), Denmark (1943-1967), Iceland (1911-1969), and Osaka (1963-1975). Mortality data were examined for the US white female population (1931-1970), England and Wales (1911-1970), Canada (1931-1970), and Japan (1947-1975). Six models were tested against the data: the first was a simple generation-effects model, and each subsequent model introduced a specific type of interaction between the age and cohort effects. After adjustment for birth cohort and year of event (incidence or mortality), the age curves from all the Western populations were similar in shape. The age curve for the Osaka incidence was similar in shape to the Western incidence curves. The Osaka curve continued to increase after menopause (MP); the post-MP decrease in rates in individual cross sections was the result of a strong cohort effect. Cohort influences are most prominent in a population in which BC incidence is changing from a low-risk profile to a high-risk profile. In a population already at high risk, secular trends in BC incidence are caused by more subtle interactions of age and cohort. The pre-MP mortality curve for Japan was similar in shape to the Western curves; however, the post-MP Japanese mortality curve had a smaller slope at each point. (50 refs)

79-1765 Epidemiology of Breast Carcinoma: Age, Menstrual Status, and Exogenous Hormone Usage in Patients with Lobular Carcinoma In Situ. (Eng) Rosen, P. P. (Dept. Pathology, Memorial Hosp., 1275 York Ave., New York, NY, 10021); Senie, R. T.; Farr, G. H.; Schottenfeld, D.; Ashikari, R. *Surgery* 85(2): 219-224; 1979.

The relationship of age, menstrual status, and exogenous hor-

mone usage to lobular carcinoma in situ (LCIS) was studied in 59 women with LCIS and 190 controls with ductal carcinoma. Thirty-nine patients had LCIS only; the other 20 had another form of carcinoma in the ipsilateral or contralateral breast in addition to LCIS. Of the 39 patients who had LCIS only, 22 were premenopausal (pre-MP), 8 were menopausal (MP), and 9 were postmenopausal (post-MP) at the time of diagnosis. Five pre-MP, three MP, and two post-MP women reported hormone usage. Of the seven patients with LCIS plus infiltrating lobular carcinoma, one was pre-MP, one was MP, and five were post-MP; three of the post-MP patients reported hormone usage. Of the 13 patients with LCIS and ductal carcinoma, 5 were pre-MP, 2 were MP, and 6 were post-MP; none reported having used hormones. Five of the 15 controls with intraductal carcinoma were pre-MP, 4 were MP, and 6 were post-MP; 6 had used hormones. Of the 175 controls with infiltrating ductal carcinoma, 35 were pre-MP, 32 were MP, and 108 were post-MP; 61 had used hormones. The data suggest that LCIS is an estrogen-dependent lesion at its inception, but all lesions may not be equally dependent on estrogens at all stages. (23 refs)

- 79-1766 Cancer in Married Couples.** (Eng) Payan, H. M. (Dept. Pathology, Bell Memorial Hosp., Ishpeming, MI, 49849). *South Med J* 72(1): 17-19; 1979.

A review of 2,512 cancer admissions in a small community hospital during a 10-yr period revealed 19 married couples with cancer. Two couples had the same type of cancer originating from the same organ (carcinoma of the breast and transitional cell carcinoma of the bladder), and 10 couples had tumors of the same histopathologic type. In 15/19 cases the cancer developed first in the wife, although the wives were younger. All 19 couples had lived together for an av of 37 yr before the first cancer was discovered. The findings underscore the importance of environment in cancer etiology. (20 refs)

- 79-1767 Pituitary Adenoma and Oral Contraceptives: A Case-Control Study.** (Eng) Coulam, C. B. (Dept. Obstetrics and Gynecology, W-10, Mayo Clinic, 200 First St., S.W., Rochester, MN, 55901); Annegers, J. F.; Aboud, C. F.; Laws, E. R.; Kurland, L. T. *Fertil Steril* 31(1): 25-28; 1979.

A case-control study was made of nine female residents of Olmsted County, Minnesota, with pituitary adenoma diagnosed between 1971 and 1977. The study was made to determine whether the use of oral contraceptives or some other etiologic factor is associated with the increasing incidence of this tumor in Olmsted County women of childbearing age. There were four controls for each patient. In this limited series, the use of oral contraceptives did not appear to be associated with the development of pituitary adenoma. Nulligravidity and nulliparity were more prevalent among the tumor patients than among the controls; smoking prior to diagnosis was reported by 5/9 patients and 16/36 controls. Other

risk factors were uncommon in both groups. Unless other etiologic agents can be identified, it appears that the increasing incidence of pituitary adenoma is due to advances in diagnostic and surgical technology rather than to a specific etiologic factor. (12 refs)

- 79-1768 The True Cancer Risk of Estrogens.** (Eng) Martin, P. L. (Dept. Obstetrics and Gynecology, Univ. California at San Diego Sch. Medicine, San Diego, CA). *Cancer Cytol* 18(2): 19-23; 1978.

The mortality experience of 159 uterine cancer patients seen in a private practice over a 30-yr period was investigated retrospectively to determine the true cancer risk of estrogen therapy. Outcome was established for 144 patients, and survival for 5 yr was considered a cure. Diagnosis was established primarily by endometrial biopsy or by dilation and curettage. Of 110 patients on long-term estrogen use before diagnosis (EU), only 1 died of recurrent cancer in <5 yr. Of 47 patients with no history of estrogen use (NEU), 7 died of recurrent disease. (Two patients whose past estrogen use could not be determined were dropped from the study.) In EU patients, diagnosis was made at an earlier stage of disease (64.2% diagnosed in situ vs 47.8% of the NEU group), and they were more likely to have a well-differentiated tumor grade than NEU patients (60% EU were Grade I vs 40% NEU). The EU patients were required to see their physicians at fairly regular intervals to obtain estrogen prescription refills and they generally reported abnormal bleeding more promptly. In the one EU patient who died, there was a change from a noninvasive well-differentiated cellular pattern found at hysterectomy to an undifferentiated pattern found at recurrence. This study indicates that estrogens, when needed, can be prescribed and monitored with reasonable safety. (6 refs)

- 79-1769 Replacement Estrogens and Endometrial Cancer.** (Eng) Jick, H. (Boston Collaborative Drug Surveillance Program, 400 Totten Pond Rd., Waltham, MA, 02154); Watkins, R. N.; Hunter, J. R.; Dinan, B. J.; Madsen, S.; Rothman, K. J.; Walker, A. M. *N Engl J Med* 300(5): 218-222; 1979.

The relationship between endometrial cancer and replacement estrogen use was investigated in a comprehensive health-care organization. Between July, 1975 and July, 1977, there was a sharp decrease in the incidence of endometrial cancer that paralleled a substantial reduction in prescriptions for replacement estrogens. Incidence rates were estimated for estrogen users and nonusers among women 50 to 64 yr old with intact uteri; current long-term users had an annual risk for endometrial cancer of 1%-3%, whereas nonusers had a risk less than one-tenth as great. These incidence rates remained fairly constant over time among users and nonusers; the drop in overall incidence soon after estrogen use declined, suggests that the increased risk associated with estrogens falls quickly after discontinuation. The reduction in incidence of

endometrial cancer in this group practice was part of a general decline in the United States after 1975. (15 refs)

- 79-1770 Carcinoma of the Prostate--An Epidemiological Report.** (Ger) Magyar, K. (Abteilung Gesundheits- und Sozialwesen, Rat der Stadt Halle, DDR-409 Halle-Neustadt, E. Germany); Heindorf, J.; Richter, C. *Z Gesamte Hyg* 24(12): 946-948; 1978.

Three hundred and twenty-four new cases of prostate carcinoma were diagnosed in the Halle area of East Germany during 1963-1972. The morbidity was 9.33/100,000 in 1963, 15.72/100,000 in 1971, and 15.55/100,000 in 1972, indicative of an increasing trend. Prostate carcinoma accounted for 2.65% of all tumors in 1963 and for 3.46% in 1972. Most patients were in the age bracket 60-80 yr at the time of diagnosis. (13 refs)

- 79-1771 Health Effects of Energy-generating Sources (2 Letters to Editor).** (Eng) Schaefer, W. W. (Sheboygan Orthopaedic Associates, SC, Sheboygan, WI); Jones, R. J. *JAMA* 241(7): 693-695; 1979.

A report by the American Medical Association Council on Scientific Affairs in which the health effects of various energy-generating sources on employees of industry and on the general public were evaluated is criticized on several counts. The study made comparisons between the most hazardous use of coal and the most favorable use of nuclear fission. Only three sources of basic statistics were used, and all three originated from the nuclear and electrical utility industry. There were no statistics on the possibility of a nuclear power plant accident with a large release of radioactivity. A rebuttal by a member of the council follows. (5 refs)

- 79-1772 Neonatal B.C.G. Vaccination and Childhood Cancer (Letter to Editor).** (Eng) Nilsson, B. S. (Dept. Thoracic Medicine, Karolinska Hosp., S-104 01 Stockholm 60, Sweden); Widstrom, O. *Lancet* 1(8109): 222; 1979.

To determine the possible effect of BCG vaccination on tumor incidence, the number of malignancies occurring in Swedish children born during 1976-1977, the year following the discontinuation of general BCG vaccination in neonates, was compared with that in children born during 1971-1972 and 1973-1974. Tumor rates for children born during 1971-1972, 1973-1974, and 1976-1977 were 17.6, 27.3, and 19.0/100,000 births, respectively, a finding that does not support the notion that BCG vaccination influences tumor incidence. (8 refs)

- 79-1773 Schizophrenia and Malignant Neoplasms in a North Swedish Population (Letter to Editor).** (Eng) Modrzewska, K. (Inst. Medical Genetics, S-752 20

Uppsala, Sweden); Book, J. A. *Lancet* 1(8110): 275-276; 1979.

Deaths due to malignant neoplasms in a North Swedish population characterized by a high degree of inbreeding and a high incidence of schizophrenia were examined. Between 1950 and 1970, 166/1,359 deaths were caused by malignancies; this ratio of 122/1,000 was significantly lower than that in the general Swedish population (163/1,000, $p < 0.003$). A biochemical and genetic link (involving perhaps catecholamine or methionine metabolism) between schizophrenia and reduced cancer risk is hypothesized. (7 refs)

- 79-1774 Morbidity Experience of Air Traffic Control Personnel--1967-1977.** (Eng) Booze, C. F. (Civil Aeromedical Inst., FAA Aeronautical Center, Oklahoma City, OK, 73125). *Avia Space Environ Med* 50(1): 1-8; 1979.

Examination of the 1967-1977 morbidity experience of 28,086 air traffic controllers (ATC) revealed that hypertension and psychoneurotic disorders were the most frequently occurring new diseases among these personnel. There was a lack of association between disease occurrence and occupation in data correlating disease occurrence with length of service and age. Among 1,759 medical disqualifications among ATC personnel during 1972-1977, malignancy ranked 9 out of 10, with a frequency of 17. (9 refs)

- 79-1775 Malignancies in Primary Immunodeficiency (ID) Diseases, with Special Emphasis on Lymphoreticular Neoplasia (Meeting Abstract).** (Eng) Frizzera, G. (Dept. Lab. Medicine and Pathology, Univ. Minnesota Medical Sch., Minneapolis, MN, 55455); Rosai, J.; Dehner, L. P.; Spector, B. D.; Kersey, J. H. *Fed Proc* 38(3, part 2): 1273; 1979. (no refs)

- 79-1776 Malignant Lymphoma of Histiocytic Type and Exposure to Phenoxyacetic Acids or Chlorophenols (Letter to Editor).** (Eng) Hardell, L. (Dept. Oncology, Univ. Hosp., S-901 85 Umea, Sweden). *Lancet* 1(8106): 55-56; 1979.

Fourteen of 17 patients with histiocytic-type malignant lymphoma admitted to the oncology department of one hospital during a 3-mo period reported current or prior employment at a job in which exposure to phenoxyacetic acids or chlorophenols may have taken place. Eleven patients reported definite exposure to the chemicals. All but 1/11 patients were exposed to chemicals containing dibenzodioxin or dibenzofuran contaminants. (4 refs)

- 79-1777 The Incidence of Head Trauma and Subsequent Risk of Seizures and Brain Tumors**

(Meeting Abstract). (Eng) Annegers, J. F. (Rochester, MN); Kurland, L. T.; Grabow, J. D.; Groover, R. V.; Laws, E. R. *Neurology (Minneapolis)* 29(4): 578; 1979. (no refs)

79-1778 Thymectomy and Cancer: A Further Report.

(Eng) Vessey, M. P. (Dept. Social and Community Medicine, Oxford Univ., Oxford, England); Doll, R.; Norman-Smith, B.; Hill, I. D. *Br J Cancer* 39(2): 193-195; 1979.

Of 419 patients who had undergone thymectomy from myasthenia gravis (MG) in selected London hospitals between 1942 and 1964, 381 were followed up through 1972. Compared with the expected value (29.8), there was a small but significant increase in the number of deaths due to all causes other than MG and thymoma (42) among these patients. Deaths due to extrathymic tumors alone were nonsignificantly increased (11 vs 8.8 expected). The most notable feature was the occurrence of seven of these deaths 10-14 yr after thymectomy, compared with only 1.9 expected. No particular type of tumor tended to develop after thymectomy, and there was no evidence that adult thymectomy was followed by an increased risk of neoplastic disease. A previous study of 2,000 patients with MC indicated that this disease itself is associated with an increased cancer risk that is reduced by thymectomy. The present study tends to negate the concept of immunologic surveillance against neoplasia. (3 refs)

79-1779 Growth Kinetics and Collagen Synthesis of Normal Skin, Normal Scar and Keloid Fibroblasts In Vitro. (Eng) Diegelmann, R. F. (Div. Plastic Surgery, Dept. Surgery, Virginia Commonwealth Univ., Medical Coll. Virginia, Richmond, VA, 23298); Cohen, I. K.; McCoy, B. J. *J Cell Physiol* 98(2): 341-346; 1979.

The growth kinetics and collagen synthesis of normal skin, normal scar, and keloid fibroblasts (FB) were studied in vitro. The mean age of the 18 keloid subjects (16 women, 4 men) was 24 yr, and all were black. Most of the keloids were from the ear lobes and the upper thorax or face. The normal skin and normal scars were from 20 subjects (11 women, 9 men) with a mean age of 35 yr; 8 were black. All normal skin and normal scars were from the facial and abdominal regions following scar revision or aesthetic surgery. The growth kinetics were the same for all groups on days 2-12. However, the keloid FB consistently synthesized two to three times more collagen per cell than either normal skin or normal scar FB

during all growth phases. There was no significant difference in absolute or relative collagen synthesis when normal skin FB from black subjects were compared with those of white subjects. However, FB derived from normal-appearing skin adjacent to keloids in two subjects had a lower level of collagen synthesis per FB than the keloid-derived FB. It is possible that: (1) keloid FB are derived from one mutant cell (monoclonal) in response to injury; (2) keloid FB have an increased differentiated capacity to synthesize collagen in response to injury secondary to mechanical or hormonal influences; or (3) keloid FB have lost the capacity to respond to a feedback signal that controls collagen synthesis during normal wound healing. (24 refs)

79-1780 Specific Alterations in Cell Cycle Control Mechanisms in Chemically Transformed Mouse Embryo Cells in Culture (Meeting Abstract). (Eng) Moses, H. L. (Mayo Clinic/Foundation, Rochester, MN, 55901); Wells, D. J.; Getz, M. J. *Fed Proc* 38(3, part 2): 1074; 1979. (no refs)

79-1781 Modulation in Cyclic AMP-dependent Plasma Membrane Phosphorylation During the Cell Cycle and Cell Differentiation is Defective in Transformed Cells (Meeting Abstract). (Eng) Scott, R. E. (Mayo Clinic, Rochester, MN, 55901). *Fed Proc* 38(3, part 2): 919; 1979. (no refs)

See also:

*(Rev.): 79-1203, 79-1204, 79-1205, 79-1219, 79-1222, 79-1226, 79-1228, 79-1229, 79-1232, 79-1234, 79-1235, 79-1240, 79-1241, 79-1242, 79-1243, 79-1244, 79-1247, 79-1254, 79-1256, 79-1269, 79-1270, 79-1272, 79-1276, 79-1277, 79-1280, 79-1282, 79-1283, 79-1284, 79-1285, 79-1286, 79-1287, 79-1288, 79-1289, 79-1290, 79-1291, 79-1292, 79-1293, 79-1294, 79-1295, 79-1296, 79-1297, 79-1298, 79-1299, 79-1300, 79-1301, 79-1302, 79-1303, 79-1304.

*(Chem.): 79-1309, 79-1323, 79-1328, 79-1339, 79-1395, 79-1465.

*(Phys.): 79-1491, 79-1497, 79-1498, 79-1499, 79-1515, 79-1520, 79-1534.

*(Viral): 79-1650.

*(Path.): 79-1733.

MISCELLANEOUS

- 79-1782 The Effects of Neonatal Tactile Stimulation on the Adult Response to Ehrlich Carcinoma in Mice.** (Eng) Dechambre, R. P. (Service d'Experimentation Animale, Institut Gustave-Roussy, 94800 Villejuif, France); LaBarba R. C. *IRCS Med Sci (Cancer)* 6(11): 472; 1978.

The effect of neonatal tactile stimulation (brushing with a sable hair brush) on the survival of C57Bl/6 mice injected with Ehrlich ascites tumor cells (5×10^6 cells) was studied. Each experimental animal was brushed daily for 10 days beginning the day after birth; controls were not brushed. Tumor cell inoculation was performed on day 48 ± 3 . The mean survival time was 24.00 days in the control group and 26.55 days in the stimulated group; the difference was significant. By 24 days after tumor inoculation, 60% of the controls and 30% of the stimulated animals had died. Thus, neonatal tactile stimulation resulted in a longer survival time after tumor graft in the adult. The data support the concept that early experience influences receptivity to transplanted tumors. (6 refs)

- 79-1783 Heterotransplantation of Human Stomach Carcinoma in Nude Mice.** (Eng) Suzuki, K. (Lab. Experimental Animals, Inst. Medical Science, Univ. Tokyo, Shiroganedai 4-6-1, Minato-ku, Tokyo 108, Japan); Sudo, K. *Gann* 70(1): 109-114; 1979.

The growth patterns of 35 primary human stomach tumors and 14 metastatic lymph nodes in nude mice were studied following sc or im transplantation. Sixteen of the primary tumors and five of the metastatic lymph nodes grew in the nude mice. Tumor takes were observed with papillary adenocarcinomas, well- and moderately well-differentiated tubular adenocarcinomas, and poorly differentiated adenocarcinomas; transplantations of mucinous adenocarcinomas, signet-ring cell carcinomas, and one adenosquamous carcinoma were unsuccessful. The histologic appearances of almost all tumors growing in the nude mice resembled those of the primary tumors. The transplants showed well-circumscribed growth patterns without aggressive invasion, especially after im transplantation. Eight tumors were maintained in serial passage for 20-39 transfers. Metastatic tumor growth in the distant lymph nodes was observed in one mouse with a primary tumor transplant and in two mice with metastatic node transplants. (7 refs)

- 79-1784 Bile Acids LVIII. Bile Acids and Colorectal Cancer.** (Eng) Davis, J. W. (Dept. Biochemistry, St. Louis Univ. Sch. Medicine, 1402 South Grand Boulevard, St. Louis, MO, 63104); Elliott, W. H. *Lipids* 13(12): 976-981; 1978.

The effects of altering the flow of bile into duodenum and of feeding diets with different lipid concentrations on the volume of bile secreted and on biliary bile acid concentrations were studied in female Sprague-Dawley rats. Two cannulas were implanted in each animal to form an externalized bile duct through which bile was drained from the common duct and returned to the duodenum. The daily mean volume of bile secreted and the daily concentrations of biliary bile acids were increased by 50% when the bile was reinfused into the rat rather than drained away. Bile drainage also reversed the diurnal fluctuation in bile acid concentration observed during bile return. The diurnal variations were markedly reduced when bile was infused into the duodenum at a uniform rate during each 24-hr period. The bile acid concentration increased as the dietary lipid concentration was increased and decreased when the dietary lipid content was reduced. (11 refs)

- 79-1785 Properties of Hybrids of Mouse Melanoma and Normal Cells (Meeting Abstract).** (Eng) Halaban, R. (Yale Univ. Sch. Medicine, New Haven, CT, 06510); Nordlund, J.; Francke, U.; Eisenstadt, J. *Fed Proc* 38(3, part 1): 784; 1979. (no refs)

- 79-1786 Effect of Dietary Cellulose on Bile Acid Levels in the Rat Small Intestine (Meeting Abstract).** (Eng) Schneeman, B. O. (Dept. Nutrition, Univ. California, Davis, CA, 95616); Gallaher, D. *Fed Proc* 38(3, part 1): 548; 1979. (no refs)

- 79-1787 Effects of Protein Nutrition on Body Weight, Serum Protein Levels and Tumor Growth (Meeting Abstract).** (Eng) Daly, J. M. (Dept. Surgery, Univ. Texas Medical Sch. at Houston, Houston, TX, 77030); Reynolds, H. M.; Rowlands, B. J.; Copeland, E. M.; Dudrick, S. J. *Fed Proc* 38(3, part 1): 864; 1979. (no refs)

- 79-1788 Correlation in the Proportion of Oleic to Vaccenic Acid of Plasma Phospholipids with the Early Stages of Hepatoma 7288CTC Growth.** (Eng) Mapes, J. P. (Dept. Biochemistry and Biophysics, Texas Agricultural Experiment Station, Texas A&M Univ. System, College Station, TX, 77843); Wood, R. *Lipids* 14(1): 70-71; 1979.

The major octadecanoate isomers oleate ($\Delta 9$) and vaccenate ($\Delta 11$) were measured in the plasma phospholipids of male Buffalo rats bearing hepatoma 7288CTC at 3-day intervals following hepatoma implantation. The percentage of vaccenate decreased from 45% of the octadecanoate fraction at day 0 to 25% by day 15 and remained at this level for the rest

of the 30-day experimental period. A significant decrease (from 45% to 35%) had occurred by day 6, well before the tumor could be detected. Therefore, early phases of hepatoma growth can be correlated with the decrease in the percentage of vaccinate. This change might have potential diagnostic value, because it can be measured in a small blood sample and because it occurs very early in the growth of the hepatoma. (10 refs)

- 79-1789 Promotion of Tumor Cell Growth by Human Platelets (Meeting Abstract).** (Eng) Hara, Y. (Div. Hematologic Res., Memorial Hosp., Providence, RI, 02860); Steiner, M.; Baldini, M. *Fed Proc* 38(3, part 2): 1307; 1979. (no refs)

- 79-1790 Altered Nucleosome Spacing in Newly Replicated Chromatin from Friend Leukemia Cells.** (Eng) Murphy, R. F. (Div. Biology, California Inst. Technology, Pasadena, CA, 91125); Wallace, R. B.; Bonner, J. *Proc Natl Acad Sci USA* 75(12): 5903-5907; 1978.

Evidence of a difference in repeat length between newly replicated and total chromatin from Friend leukemia cells (clone FSD-3) is presented. Staphylococcal nuclease digestion of DNA in isolated nuclei from cells labeled for 24 hr with ¹⁴C-thymidine and then for 10 min with ³H-thymidine indicated that the newly replicated chromatin was converted into nucleosomes at less than half the rate total chromatin is converted. This difference in digestion rate was suggested to be due to a difference in the structure of newly replicated chromatin. Polyacrylamide gel electrophoresis of nucleosomal DNA from cells labeled with ¹⁴C-thymidine for 24 hr followed by ³H-thymidine or 10 min showed that the internucleosomal spacer of newly replicated chromatin is approx 20 base pairs shorter than that of total chromatin. This difference may have implications for models of chromatin replication and transcription. (30 refs)

- 79-1791 Gastrulation in the Mouse; Assessment of Cell Populations in the Epiblast of *tw18/tw18* Embryos.** (Eng) Snow, M. H. (MRC Mammalian Development Unit, Wolfson House, Univ. Coll. London, 4 Stephenson Way, London NW1 2HE, England); Bennett, D. *J Embryol Exp Morphol* 47: 39-52; 1978.

Cell populations and mitotic activity were analyzed in embryos from seven mouse litters resulting from the mating of heterozygous mice (+/*tw18*) and taken on gestation days 6.25-7. Growth rate was analyzed by determining cell number increase and by mapping mitotic activity and planes of cleavage. Mutant (*tw18/tw18*) and normal embryos could be distinguished by morphological criteria in litters ≥ 6.75 days old. The mutant embryos were smaller but showed a very high overall mitotic activity, approx double that of their normal littermates. The mutant embryos also had a marked disorientation of the cleavage planes in most of the epiblast. In

preprimitive streak embryos (6.25 days), before any gross abnormality was detectable, two types of embryo were seen. One was comprised of small embryos that also showed the mitotic disturbances seen in the later-stage mutants, and the other consisted of larger embryos that did not show mitotic abnormalities. This observation indicates that the *tw18* allele acts several hours before primitive streak formation. There was no difference in the rate of cell death between mutant and normal embryos until 6.75 days. This suggests that arrest in division accounts for the elevated mitotic index in mutants. A small region of the epiblast (proliferative zone) in mutant embryos is free of the mitotic abnormalities characteristic of the tissue as a whole. It is suggested that some of the ectoderm of the later embryos is produced from this region. (13 refs)

- 79-1792 Participation of Cultured Teratocarcinoma Cells in Mouse Embryogenesis.** (Eng) Papaioannou, V. E. (Dept. Zoology, Oxford Univ., South Parks Road, Oxford, OX1 3PS, England); Gardner, R. L.; McBurney, M. W.; Babinet, C.; Evans, M. J. *J Embryol Exp Morphol* 44: 93-104; 1978.

The fate of embryonal carcinoma cells from four in vitro cell lines was studied following microsurgical injection of the cells into genetically dissimilar AG/Cam mouse blastocysts. The blastocysts were allowed to develop to term, and the offspring were analyzed for chimerism using coat color markers and isozyme differences in glucose phosphate isomerase. When injected into blastocysts, cell line C86 produced tumors in 6/74 offspring. The tumors, which were detected at birth, were poorly differentiated neuroectodermal teratocarcinomas. The injection of cell line C17 produced 13 chimeras in 77 offspring. Five showed chimerism only in normal tissues, mainly melanocytes of the coat and eye; the other eight chimeras developed tumors. Seven of these developed in adults and were mainly fibrosarcomas. Cell line SIKR-OSB resulted in 1 normal chimera among 44 mice born. Among 86 animals developing to term following injection of PCC3/A/1, there was 1 chimera with a small tumor and 3 normal chimeras. The levels of chimerism were usually low. In test breeding experiments, there was no evidence of germ line chimerism. It is also relevant that the four cell lines had abnormal karyotypes, as seen by G-banding, in spite of normal or near-normal chromosome numbers. This may put the cells at some disadvantage in the embryo or render them incapable of forming functional gametes. Another important factor for the incorporation of cells into the embryo is the difference in cell cycle times between the embryo and the injected cells. (18 refs)

- 79-1793 Organ Culture as an In Vitro Test for Tumorigenic Cells.** (Eng) O'Donnell, R. W. (George Washington Univ., Washington, DC, 20006). *Diss Abstr Int B* 39(8): 3685; 1979. (1 ref)

79-1794 Reciprocal Control of Membrane Permeability of Transformed Cultures of Mouse Cell Lines by External and Internal ATP. (Eng) Rozenfurt, E. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Heppel, L. A. *J Biol Chem* 254(3): 708-714; 1979.

The regulation of membrane permeability in transformed (3T6 and SV3T3) and untransformed (3T3) mouse cells by ATP was studied. External ATP applied to transformed cultures caused a rapid efflux of acid-soluble pools, as measured by labeling with ³H-uridine, ³H-adenosine, or ³H-deoxyglucose. The max effect was achieved with 0.5 mM ATP; 0.05 mM had little or no effect. Low concentrations of uncouplers, energy transfer inhibitors, or inhibitors of respiration caused a synergistic effect when combined with low concentrations of ATP, and a massive stimulation of efflux resulted. The synergistic effect was observed with a wide variety of inhibitors, all of which were able to lower the concentration of intracellular ATP. A good correlation existed between reduction in ATP levels by the inhibitors and the synergistic effect. The synergistic effect of the inhibitors was prevented by glucose, which interferes with the reduction of intracellular ATP. These inhibitors caused a small stimulation of efflux in untransformed 3T3 cells, but ATP had no effect and there was no synergism observed. Oligomycin alone caused an immediate and massive efflux of pools in 3T3 cells and was not inhibited by glucose; it appeared that this was an effect peculiar to this compound and not a general property of uncouplers and energy inhibitors. It is postulated that the formation of a channel allowing efflux of acid-soluble pools is somehow determined by the levels of both extracellular and intracellular ATP. This channel is sealed in transformed cultures at neutral pH by an energy-requiring mechanism. (33 refs)

79-1795 Active Synthesis of Collagen by Albumin-producing Liver Parenchymal Cell Clones in Culture. (Eng) Hata, R. (Dept. Tissue Physiology, Medical Res. Inst., Tokyo Medical and Dental Univ., Tokyo 101, Japan); Ninomiya, Y.; Nagai, Y.; Sakakibara, K.; Tsukada, Y. *Proc Jpn Acad Ser B* 54(7): 391-396; 1978.

Two albumin-producing rat liver parenchymal epithelial cell clones (BB and BC) synthesized collagen at a level comprising 1.1%-2.0% of the total proteins. This level was two to nine times higher than that produced by two transformed fibroblastic cell lines from mouse skin and rat lung, respectively. BB and BC synthesized types I, X, and Y collagen, but a transformed rat liver epithelial cell line synthesized only I and X. (18 refs)

79-1796 A Survey of Growth in Soft Agar and Cell Surface Properties as Markers for Transformation in Adult Rat Liver Epithelial-like Cell Cultures. (Eng) San, R. H. (British Columbia Cancer Res. Centre, Vancouver, British Columbia, Canada); Laspia, M. F.; Soiefer, A. I.

Maslansky, C. J.; Rice, J. M.; Williams, G. M. *Cancer Res* 39(3): 1026-1034; 1979.

Growth in soft agar and five cell membrane properties were evaluated as markers for transformation in nine normal adult rat liver (ARL) and four hepatocarcinoma continuous epithelial-like cell lines. Seven of the nine ARL lines did not produce tumors in nude mice, but two (ARL 6 and ARL 17) were tumorigenic. Hepatocarcinoma lines HTC, ND-HC1, and MH₁C₁ were tumorigenic, but RH35 was not. Growth in soft agar was a specific and sensitive marker for transformation, but high uptake of 2-deoxy-D-glucose was specific but not sensitive. Agglutination and hemadsorption mediated by concanavalin A, multinucleation in the presence of cytochalasin B, and the presence of Mg²⁺-dependent ATPase activity did not correlate with tumorigenicity or with the other markers. Some of the lines were found to be carrying an occult infection by *Mycoplasma hyorhinis*, a porcine organism. The infection did not affect any of the properties studied, including tumorigenicity in nude mice, and it was eliminated by passage of the infected cells through nude mice. (63 refs)

79-1797 Identification of Transformed Rat Liver Epithelial Cells in Cultures. (Eng) Iype, P. T. (Paterson Labs., Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England); Allen, T. D. *Cancer Lett* 6(1): 27-32; 1979.

The growth potential of normal rat liver cells, rat liver epithelial cells transformed in vitro (chemically or spontaneously), and cells from a malignant hepatoma induced chemically in vivo was investigated under various experimental conditions. The control cells failed to form colonies over a base layer of living parent cells, whereas the transformed cells formed distinct colonies. Contact with living normal liver cells was required for the growth inhibition of the untransformed cells, as normal cells did produce regular colonies over a base layer prefixed with glutaraldehyde. The hepatoma cells exhibited signs of invasion in vitro in that they formed distinct colonies, surrounded by a highly stained area, on the base layers of normal cells. The fact that some of the in vitro-transformed liver cells formed compact colonies in the live base layer indicates that although these cells are no longer under the proliferation control exerted by normal cells, they have not yet acquired invasiveness. The altered properties of hepatic cells during the early stages of transformation can be assessed by plating these cells over a living base layer of normal liver cells. This method is believed to score the premalignant (anchorage-dependent) and fully transformed (anchorage-independent) liver cells. (11 refs)

79-1798 Establishment of a Rat Hepatoma Cell Line Which Has Ornithine Carbamoyltransferase Activity and Grows Continuously in Arginine-derived Medium. (Eng) Niwa, A. (Dept. Microbiology, Dokkyo Univ. Sch.

Medicine, Mibu, Tochigi 321-02, Japan); Yamamoto, K.; Yasumura, Y. *J Cell Physiol* 98(1): 177-184; 1979.

An ornithine carbamoyltransferase (OCT)-positive subline was developed from an epithelial cell line (H4-II-E, derived from the Reuber hepatoma H35) that has no significant OCT activity, by a multistep procedure. H4-II-E cells were exposed to gradually increasing concentrations of 5-bromo-deoxyuridine and then adapted to grow in medium in which glutamic acid was substituted for glutamine. The adapted cells were cultured in arginine-deprived medium for several mo before cell colonies were observed. Thereafter, the cell colonies were transferred at 10-day intervals and grown continuously in arginine-deprived ornithine-supplemented medium for >2 yr. The growth of the cells was effectively controlled by varying the ornithine concentration between 0.03 and 1 mM. The population of attached cells and OCT activity per culture dish were nearly constant at 2 mg cell protein (5×10^6 cells) and 100 units (50 units/mg protein), respectively, for as long as the cultures were maintained. These patterns of growth and OCT activity were constant in subsequent subcultures. These may be the only serially cultivated cells that have significant levels of OCT activity and can be grown in ornithine-supplemented arginine-deficient media. (21 refs)

79-1799 Establishment and Characterization of Primary Human Pancreatic Carcinoma in Continuous Cell Culture and in Nude Mice. (Eng) Grant, A. G. (Dept. Surgery, St. George's Hosp. Medical Sch., Cranmer Terrace, London SW17 0RE, England); Duke, D.; Hermon-Taylor, J. *Br J Cancer* 39(2): 143-151; 1979.

A primary human pancreatic exocrine adenocarcinoma established in tissue culture and xenografts established in im-

mune-deficient nu/nu mice were characterized. The primary tumor cells grew as an epithelioid monolayer without fibroblast contamination; density-dependent inhibition of cell growth was not observed at confluence. The doubling time stabilized at 36 hr after the 11th passage. Approx 10%-15% of the total cell population was accounted for by cells floating free in suspension; <1% of these cells formed new colonies after reseeding. Evidence of tumor origin was provided by a modal chromosome number of 62. The tumorigenicity of the cells was indicated by growth on a confluent monolayer of early passage diploid fibroblasts and in soft agar, and as solid tumors in nude mice. No growth was obtained with floating cells or fibroblasts. Xenografts established from the cell line or directly from primary tumor tissue retained the histology of the original tumor upon serial transplantation. The tumor cell line and the xenografts lacked the normal human pancreatic digestive enzymes, but it did exhibit glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, phosphoglucose isomerase, phosphoglucomutase, carbonic anhydrase, and alkaline phosphatase activities. (13 refs)

79-1800 Fibrorectosigmoidoscopy. Results in 476 Cases. (Fre) Lambert, R. (Centre d'Endoscopie, Pavillon H, Hopital E. Herriot, F 69374 Lyon Cedex 2, France); Olive, C.; Chabanon, M.; Chabanon, R. *Nouv Presse Med* 7(46): 4213-4215; 1978.

Four hundred and seventy-six patients with or without digestive symptoms were examined by a 60-cm fiber rectosigmoidoscope. Nontumorous lesions were found in 44 patients, tumors in 105 (125 adenomas and 31 carcinomas). Seventy-one tumors (50 adenomas and 21 carcinomas) were in the area accessible to rigid rectosigmoidoscopy (0-19 cm); the other 85 tumors were beyond this area. (4 refs)

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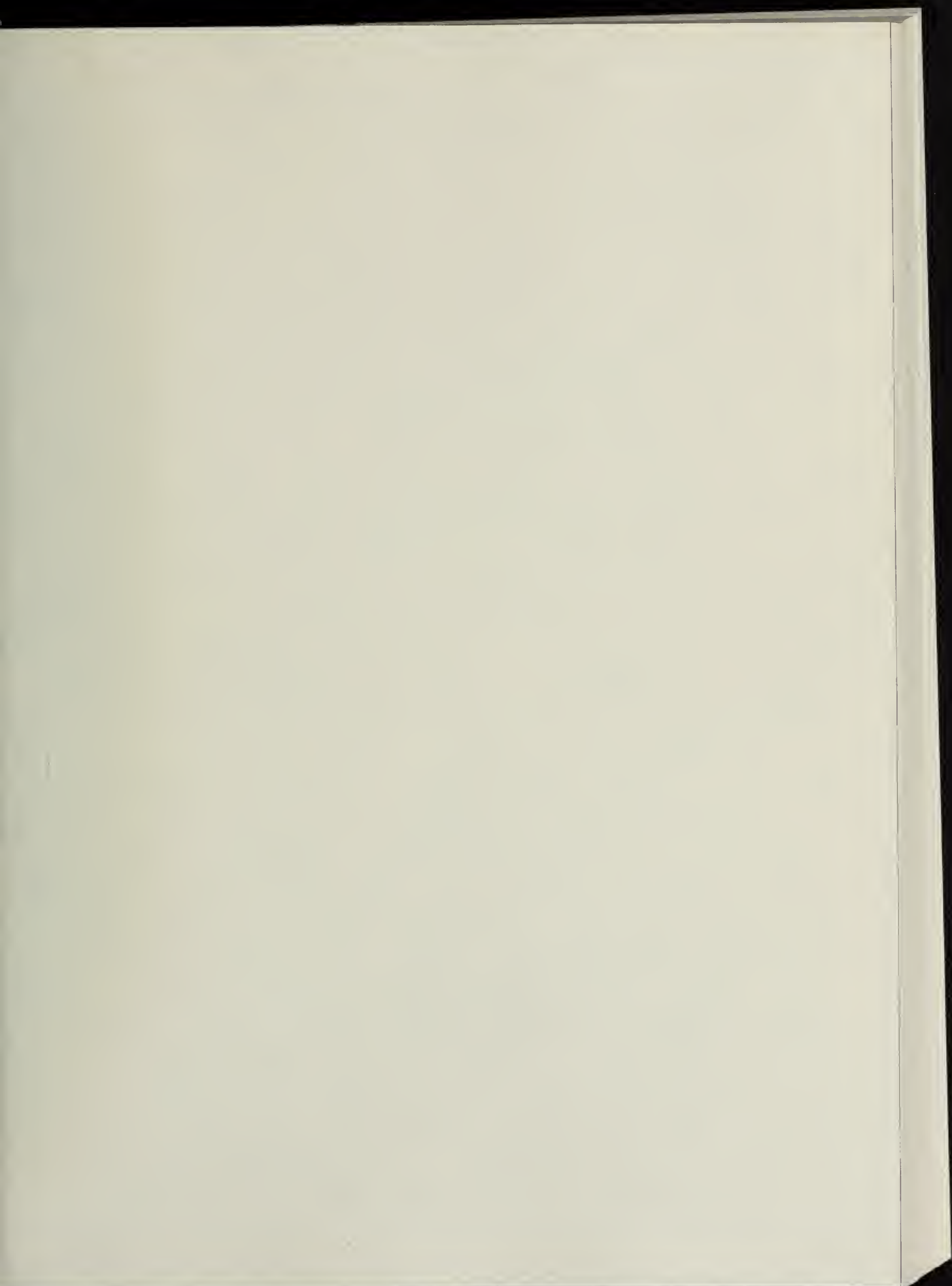
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CARCINOGENESIS ABSTRACTS

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CARCINOGENESIS ABSTRACTS

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ABBREVIATIONS

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LANGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

ABBREVIATIONS used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μl	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μCi	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED₅₀	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO₂	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μg	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intra-dermal	SGOT	serum glutamic-oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT	serum glutamic-pyruvic transaminase
IgB	Immunoglobulin B	soln	solution
IgG	Immunoglobulin G	TCD	tissue culture dose
IgM	Immunoglobulin M	TCD₅₀	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intraperitoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
Km	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD₅₀	median lethal dose		
M	molar		
μM	micromolar		

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REVIEW

- 79-1801 Differentiation of Normal and Neoplastic Hematopoietic Cells: A Summary.** (Eng) Clarkson, B. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021). *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 953-967; 1978.

Recent developments in various fields related to the differentiation of normal and neoplastic hematopoietic cells are summarized. Topics discussed include: ontogeny of hematopoietic development, attempts to isolate hematopoietic stem cells and define their properties, genetic control of antigenic expression of normal and transformed cells, regulation of hematopoietic differentiation, influence of viruses on transformation and differentiation, clinicopathological pathways, the development and integration of the immune system, and the use of newly recognized cell markers for defining the origins and abnormalities of specific cell types involved in various hematopoietic diseases. The interrelatedness of different research areas is emphasized. (no refs)

- 79-1802 Erythroleukemia Cells: Commitment to Differentiate the Role of the Cell Surface.** (Eng) Rifkind, R. A. (Cancer Center, Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032); Fibach, E.; Reuben, R. C.; Gazitt, Y.; Yamasaki, H.; Weinstein, I. B.; Nudel, U.; Sumida, I.; Terada, M.; Marks, P. A. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book A), 528 pp.; 209-220; 1978.

Evidence indicating there are two components to induced differentiation, the commitment of murine erythroleukemia cells (MELC) to erythropoietic differentiation and the program that coordinates the series of biosynthetic and morphogenetic events that constitute the actual expression of the erythropoietic developmental process, is reviewed, along with evidence indicating that alterations of the plasma membrane may be implicated in the induction of differentiation by some agents. Commitment was responsive to the concentration of hexamethylene bisacetamide (HMBA), but expression was not. When MELC were exposed continuously to HMBA, benzidine-reactive, Hb-containing cells were detectable in the culture after 48 hr. When MELC were suspended in HMBA for various times (5-100 hr) and transferred to a fresh medium free of HMBA, commitment was detected after 24 hr. When MELC were cultured with HMBA and transferred to inducer-free semisolid media, commitment was detected at 12-16 hr. The number of cells in the colony was related to the proportion of benzidine-reactive cells in the colony. MELC strains D519 and DR10 had an increased cyclic AMP content when exposed to certain inducing agents, implicating

plasma membrane or plasma membrane-related functions in commitment. To determine the relationship between 12-O-tetradecanoylphorbol-13-acetate (TPA)-mediated inhibition of differentiation and commitment to differentiation, TPA was added to MELC at various times after the addition of HMBA. Max inhibition of differentiation occurred even when TPA was added up to 24 hr after HMBA, suggesting that TPA can only inhibit differentiation of cells that have not yet passed a critical step related to commitment. Thus, a wide variety of agents can alter significantly the probability for commitment to and expression of the program of erythropoietic differentiation in MELC. Some agents may have a primary effect at the plasma membrane level. The unique properties of the individual inducing agents may reflect various potential sites of interaction between inducing agents and the sequential steps of the common pathway for the regulation of erythropoietic differentiation. (45 refs)

- 79-1803 Biology of the Human Malignant Lymphomas. V. Differentiation and Neoplastic Properties of Established Lymphoma Cell Lines.** (Eng) Epstein, A. L. (Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305); Kaplan, H. S. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 915-934; 1978.

The maintenance of the differentiated state of malignant lymphoma cells established in vitro is reviewed, along with the neoplastic properties of these cells. Malignant lymphomas were grown on agar and multiple clones were isolated from individual cell lines. The clonal subpopulations maintained the differentiated traits of the parent cell lines; however, certain clones expressed specific receptors with increased frequencies, indicating that the genes responsible for these traits could be segregated by cloning techniques. The malignant cells continued to express normal differentiation antigens, surface receptors, and functional capabilities in vitro. Diffuse histiocytic and undifferentiated lymphoma cells initially had a cloning efficiency of <1% when 0.5% Noble agar was used as a substrate. In the presence of human serum and selected feeder monolayers, however, the cloning efficiencies increased to 15%-25%. Supplements such as dithiothreitol, 2-mercaptoethanol, and pleural effusion fluids produced concentration-dependent increases in cloning efficiency. For a given cell line, cells plated on the agar surface and in semisolid agar suspension had identical cloning efficiencies. The cloning efficiencies of individual cell lines increased from <1% to approx 50% after a single passage on agar. The applicability of experimental criteria for determining the malignant nature of cultured mammalian fibroblasts to malignant

cells of lymphoid tissue origin was assessed. The potential use of malignant lymphoma cells for clinical and basic biological research is considered. (109 refs)

- 79-1804 Potential of Plant Genetic Systems for Monitoring and Screening Mutagens.** (Eng) Nilan, R. A. (Program in Genetics, Washington State Univ., Pullman, WA, 99164). *Environ Health Perspect* 27: 181-196; 1978.

The scope and potential of plant genetic systems for mutagenesis research are reviewed. There are about a dozen reliable plant genetic systems that can increase the scope and effectiveness of chemical and physical mutagen screening and monitoring procedures. Major advantages of these systems relate to their reproductive nature, easy culture, and growth habits. Plants are the only systems now in use as monitors of genetic effects caused by air pollution and pesticides. (126 refs)

- 79-1805 Introduction: Utilization of Higher Plant Systems as Monitors of Environmental Mutagens.** (Eng) de Serres, F. J. (Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709). *Environ Health Perspect* 27: 3-6; 1978.

A workshop was organized to review the major problems in environmental mutagenesis, to provide illustrative examples of areas where various plant systems have already been put to use, and to identify additional approaches for research. The relationship between mutagenicity and carcinogenicity is illustrated by experience with 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide, a nitrofur derivative used as a food preservative in Japan. This chemical was found to be mutagenic in cultured bacterial, human, yeast, and *Neurospora* cells and to produce stomach cancer in mice. Investigations in the US, England, and Japan have shown that 90%-95% of chemical carcinogens are also mutagens. Research in environmental mutagenesis and genetic toxicology is divided into four main areas: basic mechanisms by which mutations are produced; development of assay systems that provide a comprehensive evaluation of chemicals in widespread use; environmental monitoring for mutagens; and evaluation of the risk of exposure to chemicals with identified potential in mass screening programs. Plant systems seem especially well-suited for research in at least the first three areas. The most promising areas for future development are plant screening tests for nondisjunction and for the evaluation of air and water pollutants. In the latter category, the *Tradescantia* stamen hair system is being used to evaluate the mutagenicity of various air pollutants. (9 refs)

- 79-1806 Mutagenicity and Water Chlorination: Prospect and Perspective.** (Eng) Cumming, R. B. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830). *Water Chlorination* 2: 411-416; 1978.

A brief overview of mutagenicity and mutagenicity testing as they are perceived today is presented, and their relevance to assessment of the impact of water chlorination on public health is shown. (6 refs)

- 79-1807 Microsomal Aspects of Carcinogenesis and Neoplasia.** (Eng) Apffel, C. A. (Ira T. Nathan-son Res. Labs., Pondville Hosp., Walpole, MA, 02081). *Med Hypotheses* 5(1): 23-52; 1979.

Microsomal aspects of carcinogenesis and neoplasia are reviewed. Carcinogenic agents initiate biophysical perturbations, chemical alterations, and conformational transitions in the membrane lattice of the endoplasmic reticulum (ER). Crucial among the malignancy-related alterations is the increased, irreversible detachment of polysomes from membranes of the rough ER. Since only attached polysomes can synthesize microsomal cytochromes, the values of these factors are decreased and mixed function oxidase activities are impaired in tumor cells that possess a monooxygenase system before malignant transformation. Consequences more broadly common to tumor cells of different categories are uncontrolled biosynthesis of cholesterol and derepressed thiol-disulfide exchange with subsequently activated synthesis of nonspecific proteins and of DNA involved in neoplastic growth. Apparently, the initial carcinogenic event destroys proteins required for polysome anchoring. As in the case of cytochrome P-450 and b5, only membrane-bound polysomes may be capable of synthesizing the attachment proteins. The destruction of the attachment sites (proteins), therefore, implies a vertical transmission of the membrane-polysome dieresis with ensuing uncontrolled growth through successive generations of cells. No permanent alteration of genetic material has to be postulated. (150 refs)

- 79-1808 Role of Biotransformation in the Toxicity of Inhalation Anesthetics.** (Eng) Vaughan, R. W. (Dept. Anesthesiology, Univ. Arizona, Coll. Medicine, Tucson, AZ, 85724); Sipes, I. G.; Brown, B. R. *Life Sci* 23(25): 2447-2462; 1979.

Subacute and chronic viscerotoxicity due to inhalation anesthetics are reviewed. The anesthetics considered are chloroform, trichloroethylene, fluroxene, methoxyflurane, halothane, enflurane, and isoflurane. Abundant evidence relates the bioactivation of xenobiotics, including these anesthetics, to highly reactive intermediates. These intermediates covalently interact with tissue macromolecules and thus alter the integrity of cells. These alterations can lead to necrosis, hypertrophy, or carcinogenesis. The interaction of a xenobiotic with DNA may predict the carcinogenic potential of the compound. This is particularly important when an individual

is subject to continuous exposures of trace amounts of the chemical. Various factors, such as excess ethanol intake or the use of drugs that induce the microsomal drug-metabolizing enzymes, may modify the biotransformation of anesthetic agents and thus increase the risk of a potential interaction with DNA. These findings indicate that it is important to know to what extent anesthetic agents undergo bioactivation and the fate of the reactive intermediates that are produced. The widespread use of these drugs in clinical anesthetic practice dictates continued intense studies. (123 refs)

- 79-1809 The Drinking Water-Cancer-Carbon Filtration Problem.** (Eng) Hyman, E. S. (3629 Prytania St., New Orleans, LA, 70115). *J La State Med Soc* 131(1): 11-32; 1979.

Information opposing the hypothesis that drinking water in the US causes cancer is presented in response to public concern about chloroform levels in New Orleans' drinking water. It is suggested that chloroform per se or as a surrogate for other halogenated organics is low on the list of potential carcinogens, especially in comparison with cigarette smoke, inhaled asbestos, or nitrosamines produced by nitrates in food. It is doubtful whether chloroform can cause cancer in rats or any other species without first destroying biochemical processes essential to the survival of most of the liver cells and overwhelming the metabolic pathways that rid the body of that agent. It is also suggested that statistical studies showing correlations between river water or chloroform and cancer are not convincing. (72 refs)

- 79-1810 Potential Halogenated Industrial Carcinogenic and Mutagenic Chemicals. I. Halogenated Unsaturated Hydrocarbons.** (Eng) Fishbein, L. (National Center Toxicological Res., Jefferson, AR, 72079). *Sci Total Environ* 11(2): 111-161; 1979.

Data on the carcinogenicity and mutagenicity of several of the most industrially significant halogenated unsaturated hydrocarbons are reviewed to assess the nature of their present potential risk. These compounds are vinyl chloride, vinylidene chloride, trichloroethylene, perchloroethylene, chloroprene, trans-1,4-dichlorobutene, hexachlorobutadiene, and allyl chloride. Aspects of their synthesis (primarily in terms of the nature of possible hazardous trace impurities), production volumes and use patterns, chemical and biological reactivity and stability, environmental occurrence, and national permissible worker exposure levels are considered. Experimental and human epidemiologic evidence of the carcinogenicity and mutagenicity of the hydrocarbons is reviewed, as are data concerning their in vivo and in vitro metabolism. (302 refs)

- 79-1811 Potential Halogenated Industrial Carcinogenic and Mutagenic Chemicals II. Halogenated Saturated Hydrocarbons.** (Eng) Fishbein, L. (Natl. Center for Toxicological Res., Jefferson, AR, 72079). *Sci Total Environ* 11(2): 163-195; 1979.

The carcinogenic and mutagenic potentials of the industrially significant halogenated saturated hydrocarbons are reviewed. These compounds possess considerable utility as solvents, drycleaning fluids, refrigerants, fumigants, degreasing agents, propellants, and intermediates in the production of other chemicals, textiles, and plastics. They include methyl chloride, methylene chloride, chloroform, carbon tetrachloride, methyl chloroform, 1,1,2-trichloroethane, hexachloroethane, ethyl chloride, and the fluorocarbons. They are discussed principally in terms of their synthesis or occurrence, areas of application, stability, distribution, reactivity, exposure levels, populations at risk, carcinogenicity, mutagenicity, and metabolism. (164 refs)

- 79-1812 Manufacturing Processes. Refining of Nickel.** (Eng) Morgan, L. G. (Medical Dept., Inco Europe Ltd., Clydach, Swansea SA6 5QR, Wales). *J Soc Occup Med* 29(1): 33-35; 1979.

Health hazards associated with processes used in refining sulfide and lateritic nickel ores are described briefly. Respiratory cancer has been associated with dusty processes in nickel refining, but this hazard has been eliminated. Nickel carbonyl gas is highly toxic; it is normally found only when nickel is refined by the carbonyl process. The gas has caused respiratory cancer in experimental animals, but there is no evidence that this is the case in humans. (4 refs)

- 79-1813 Dietary Polyunsaturated Fat Versus Saturated Fat in Relation to Mammary Carcinogenesis.** (Eng) Carroll, K. K. (Dept. Biochemistry, Univ. Western Ontario, London, Ontario, Canada, N6A 5C1); Hopkins, G. J. *Lipids* 14(2): 155-158; 1979.

The relationship between dietary fat and mammary carcinogenesis is reviewed. Experiments in rats and mice showed that animals fed high-fat diets were more susceptible to spontaneous and carcinogen-induced mammary tumors than those fed low-fat diets. Apparently, dietary fat acted as a promoter rather than an initiator of tumors. Unsaturated fats enhanced mammary tumorigenesis to a greater extent than did saturated fats, although there was no direct correlation between degree of unsaturation and mammary tumor yield. Breast cancer mortality among humans in different countries showed a positive correlation with total fat intake, a somewhat smaller positive correlation with animal fat intake, and no correlation with vegetable fat intake. The fact that Japanese women consume a more unsaturated type of fat than Americans but have a lower incidence of breast cancer fits in with experi-

mental data showing a requirement for polyunsaturated oil in mammary tumorigenesis that is not satisfied by fats such as coconut oil or beef tallow but is satisfied by adding 3% sunflower seed oil to these fats. There is an overall requirement for a high-fat diet in addition to the polyunsaturated fat. Most human diets probably supply sufficient polyunsaturated fat to achieve the promoting effect in the animal model. It should be possible to reduce breast cancer incidence and mortality by reducing the intake of meat, milk products, margarines, shortenings, and salad oils. (21 refs)

- 79-1814 Drug Interactions in the Intestinal Tract.** (Ger) Mitznegg, P. (Institut für Pharmakologie und Toxikologie, Universität Erlangen-Nürnberg, Universitätsstrasse 22, 8520 Erlangen, W. Germany). *Fortschr Med* 97(8): 315-317; 1979.

Mechanisms of drug interactions in the gastrointestinal tract are reviewed briefly. The combination of paraffin-containing laxatives and the emulsifier sodium dioctyl sulfosuccinate (sometimes present in laxatives) should be avoided, as it may lead to the formation of foreign-body granulomas with possible subsequent degeneration to malignancy. (5 refs)

- 79-1815 Experimental Colon Carcinogenesis.** (Eng) Zedek, M. S. (Lab. Pharmacology, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021). *Gastrointest Tract Cancer* 343-360; 1978.

Studies of the sensitivity of colonic epithelium to the induction of tumors by methylazoxymethanol (MAM), dimethylhydrazine (DMH), azoxymethane (AOM), N-methyl-N'-nitronitrosoguanidine (MNNG), or N-methyl-N-nitrosourea (MNU) are reviewed, along with evidence of the role of dietary factors, intestinal flora, and bile acids in colon cancer induction. The common feature of the colon carcinogens (CCG) is the eventual formation of a methylating moiety. However, slight modification of the structure of these compounds results in compounds that cannot be activated to CCG. CCG are effectively transported to their target sites via the circulation. They do not require transport by the bile or metabolism by intestinal flora to exert their biological effects. Several findings indicate that the target tissues directly convert the parent compounds into ultimate carcinogens. The fact that a single treatment with MAM acetate induces more tumors of the colon than of the duodenum or cecum, even though DNA synthesis in each of these tissues is inhibited similarly, suggests that other factors play a modifying role in tumor development. In this regard, several investigations indicate that bile acids and/or bacteria may influence colon tumor formation. The finding that small intestine and colon respond similarly to the toxic effects of 5-fluorouracil and nitrogen mustard exaggerates even further the selective resistance of jejunum and ileum to the carcinogen-induced lesions. Relationships found between age and sensitivity to tumor in-

duction may prove significant in view of the suggestion that metabolic processes, the activity of which may be age-related, may enhance the degradation of MAM to its ultimate carcinogenic form. It has been shown that CCG can interact with nucleic acids and that DNA strand breakage can occur and, in some cases, persist for prolonged periods. Information regarding the mechanism of cell detachment at the mucosal surface of the intestine and the effects of CCG on this process may prove useful in understanding polyp formation. (85 refs)

- 79-1816 Unit of Environmental Carcinogens.** (Eng) Griciute, L. (International Agency Res. Cancer, Lyon, France). *IARC Annual Report* 44-65; 1978.

The 1978 activities of the Unit of Environmental Carcinogens of the International Agency for Research on Cancer are reported. The unit is continuing to elaborate and standardize techniques for analyzing environmental carcinogens and to measure these substances in environmental samples. A collaborative study is being made of methods for analyzing volatile and nonvolatile N-nitrosamines (NA's) and an aflatoxin sample check survey was started. Various environmental samples (alcoholic beverages, experimental animal feed, urine samples in areas with endemic urinary bladder cancer, tobacco smoke, pharmaceutical formulations, and bread) are being analyzed for NA's and other chemical carcinogens. *In vivo* formation of NA's was studied in the laboratory, by investigating the role of phenols in nitrosation, and in the field, by determining nitrite levels in salivas of the population of the Caspian littoral with differing esophageal cancer morbidity. Collaborative studies of the relation between asbestos and cancer and of the combined action of benzo(a)pyrene, N-nitrosodiethylamine, and aflatoxin B₁ at low, marginally active doses are being conducted. The latter study is designed to elucidate the behavior of several chemicals in the same environmental sample. Carcinogenicity testing of the antileprosy drug dapsone in rats and mice revealed that dapsone is slightly carcinogenic in these rodents. Fibrosarcomas and angiosarcomas of the spleen were seen in rats, mostly in males, along with cancers of the thyroid. Hemangiosarcomas of the liver were noted in mice. The tumors occurred during the second year of the experiment. (19 refs)

- 79-1817 Unit of Chemical Carcinogenesis.** (Eng) Tomatis, L. (International Agency Res. Cancer, Lyon, France). *IARC Annual Report* 77-113; 1978.

The activities of the Unit of Chemical Carcinogenesis of the International Agency for Research on Cancer (IARC) continue to be concerned with identifying potentially carcinogenic chemicals in the environment and evaluating their risk to humans, and developing criteria for better assessment of the significance of experimental results in predicting similar effects in humans. A detailed summary of these activities by various investigators is given. Up to September 1978, 19

volumes of IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans have been published. A total of 420 chemicals have been evaluated. Evidence or a strong suspicion of a causal association with cancer in humans was found for 26 chemicals; for a further 19 chemicals, no evaluation of a carcinogenic risk to humans was made since the available data were inconclusive. These chemicals are tabulated, along with chemicals for which there is sufficient evidence of carcinogenicity in experimental animals. The general paucity of epidemiological studies and inadequacies in several experimental reports were among the greatest difficulties encountered during compilation of the monographs. Criteria for carrying out and reporting long and short-term carcinogenicity experiments and related tests are being drafted to make published results universally acceptable. A worldwide survey of chemicals being tested for carcinogenicity is being continued, with the aims of avoiding unnecessary duplication of research, of increasing communication among scientists, and of making a census of available research facilities and of the chemicals being tested. (64 refs)

- 79-1818 Cocarcinogenesis.** (Eng) Sivak, A. (Biomedical Sciences Section, Arthur D. Little, Inc., Cambridge, MA, 02140). *Biochim Biophys Acta* 560(1): 67-89; 1979.

The role of exogenous chemical agents, viruses, the immune system, nutritional factors, and hormones as cocarcinogens in animals and humans is reviewed. Cocarcinogenic (CC) effects of exogenous chemicals have been demonstrated in mouse skin, rat liver, rat and dog bladder, rat gastrointestinal tract, and mouse and hamster lung. The discovery of excess deaths from lung cancer among uranium miners who are also cigarette smokers suggests a CC effect. Cell culture systems have been developed to demonstrate tumor promotion, a special case of CC. RNA tumor viruses are CC with 3-methylcholanthrene in mice. Hepatitis B virus appears to be involved, along with other factors, in human hepatic carcinoma, especially in tropical Asia and Africa. Nasal instillation of influenza virus has a CC influence in the mouse lung with inhalation of a polycyclic aromatic hydrocarbon aerosol or diethylnitrosamine in the drinking water. No clear explanation has been found for the tumor-enhancing or CC effect of immune system reactions, but it appears to be the result of a low-level immune response. Suboptimal levels of even a single nutrient may have a strong influence on tumor induction by a carcinogen. In animal systems and clinical situations, the growth of mammary and prostate tumors can be modulated by hormone treatment. Although CC has been demonstrated repeatedly, the specific cellular and biochemical processes involved are poorly understood. (182 refs)

- 79-1819 Experimental Carcinogenesis of Antitumour Drugs.** (Eng) Schmahl, D. (Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Neuenheimer

Feld 280, D-6900 Heidelberg, W. Germany); Habs, M. *Cancer Treat Rev* 5(4): 175-184; 1978.

The carcinogenic potential of anticancer chemotherapeutic agents is reviewed. These drugs have been evaluated in mice, rats, monkeys and hamsters. Alkylating agents, including 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide, uracil mustard, procarbazine, and cyclophosphamide, have a relatively strong carcinogenic action, as do the nitrosoureas. However, nitrosourea analogs with good antitumor activity and reduced carcinogenicity (eg, 1-(2-hydroxyethyl)-3-(2-chloroethyl)-3-nitrosourea) also exist. Although studies of the carcinogenicity of antimetabolites and antimitotic agents have produced contradictory results, these compounds appear to be less carcinogenic than the alkylating agents. Among the carcinostatic antibiotics, strong carcinogenic effects have been reported for adriamycin, rubidomycin, daunomycin, and mitomycin C. Combinations of anticancer drugs appear to be less carcinogenic than the same drugs individually. The induction times of the tumors induced by anticancer drugs are dose-dependent, and the organs affected may be specific (bladder cancer is caused by low doses of cyclophosphamide) or nonspecific (alkylating agents induce cancer in various organs). (63 refs)

- 79-1820 Camphor USP.** (Eng) Opdyke, D. L. (Res. Inst. Fragrance Materials, Inc., Englewood Cliffs, NJ, 07632). *Food Cosmet Toxicol* 16(Suppl 1): 665-671; 1978.

The structure, occurrence, preparation, and commercial uses of camphor are reviewed, and biological data concerning toxicity, inhalation effects, irritation, sensitization, metabolism, carcinogenicity, cytotoxicity, phytotoxicity, pharmacology, and effects on invertebrates are presented. The results of studies in which camphor was applied topically or injected ip in mice suggest that it is noncarcinogenic. (133 refs)

- 79-1821 Standards Corner.** (Eng) Anonymous (NIO-SH, Parklawn Bldg., 5600 Fishers Lane, Rockville, MD, 20852). *Occup Hazards* 41(2): 71-74; 1979.

The National Institute for Occupational Safety and Health (NIOSH) has issued a criteria document to the Occupational Safety and Health Administration warning that the dyestuff o-toluidine be kept below a ceiling concentration of $20 \mu\text{g}/\text{m}^3$ of air over a 60-min sampling period, that skin contact with the chemical be minimized, and that stringent engineering controls and controlled entry into areas where o-toluidine is handled or stored be enforced. o-Toluidine is an analog of benzidine. Both compounds have been shown to cause cancer in various organs of laboratory animals. In addition, epidemiological studies showed that workers who had been exposed to both compounds developed bladder cancer. NIOSH has also published a warning of the possible adverse effects of glycidyl ethers on the testes and blood-forming system and

has recommended that worker exposures to a group of diisocyanate monomers be limited. Epichlorohydrin has been identified by NIOSH as a potential human carcinogen, and it has been recommended that worker exposure to it be minimized and skin contact avoided. (no refs)

79-1822 The Stilbestrol Problem--Chairman's Report.

(Eng) Mattingly, R. F. (Dept. Gynecology and Obstetrics, Medical Coll. Wisconsin, 8700 W. Wisconsin Ave., Milwaukee, WI, 53226). In: *Cervical Pathology and Colposcopy. Selected Papers from the Second World Congress of Cervical Pathology and Colposcopy held in Graz, Austria, 15-18 October 1975*. Burghardt, E.; Holzer, E.; Jordan, J. A., eds. (Stuttgart: Georg Thieme Publishers): 146 pp.; 85-87; 1978.

The relationship between intrauterine diethylstilbestrol exposure and development of vaginal adenosis is briefly reviewed. (no refs)

79-1823 Colposcopic and Histological Findings in Stilbestrol-exposed Women. (Eng) Stafl, A. (Dept. Gynecology and Obstetrics, Medical Coll. Wisconsin, 8700 W. Wisconsin Ave., Milwaukee, WI, 53226). In: *Cervical Pathology and Colposcopy. Selected Papers from the Second World Congress of Cervical Pathology and Colposcopy held in Graz, Austria, 15-18 October 1975*. Burghardt, E.; Holzer, E.; Jordan, J. A., eds. (Stuttgart: Georg Thieme Publishers): 146 pp.; pp. 82-85; 1978.

Colposcopic examination of 280 young women whose mothers received diethylstilbestrol (DES) during the first trimester of pregnancy revealed vaginal adenosis in 231. Examination of the latter revealed that 96% had an abnormal colposcopic lesion, an incidence that was significantly higher than the 8% incidence of abnormal colposcopic lesions on the cervix of girls who were not exposed to DES. The results of studies concerning the morphogenesis of cervical neoplasias are summarized. (no refs)

79-1824 Prolactin and Human Breast Cancer: A Review.

(Eng) Nagasawa, H. (Pharmacology Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan). *Eur J Cancer* 15(3): 267-279; 1979.

The relationship between human prolactin (hPRL) and breast cancer (BC) is reviewed. A positive correlation between age and hPRL in cystic breast disease has been shown, but, although disordered hPRL regulation has been found in women with BC, its significance in the etiology of BC is uncertain. hPRL secretion varies according to age, stage in the menstrual cycle, and pregnancy. Certain drugs, including estrogenic agents and rauwolfia derivatives, stimulate pituitary

hPRL secretion, but the connection between these drugs and BC is at best uncertain. Serum prolactin levels have been reported to vary with race and to be elevated in close relatives of BC patients, but other studies have not supported these findings. Similarly, the relationship between BC and hPRL in the breast fluid or breast cyst fluid remains to be investigated, as does the possible relationship between BC and the ability of hPRL to stimulate the secretion of dehydroepiandrosterone. Studies have found that some BC's are sensitive to hPRL, and the existence of hPRL receptors in human breast tissues has been hypothesized. Also, factors that decrease prolactin secretion (eg, L-dopa and hypophysectomy) have often brought about regression of BC. Further research is needed to establish unequivocally the role of hPRL in human BC. (126 refs)

79-1825 Estrogens During Menopause and the Risk of Endometrial Carcinoma. (Ger) Lachnit-Fixon, U. (Department fur Gynakologische Endokrinologie, Schering AG, Mullerstrasse 170-178, D-1000 Berlin 65, W. Germany). *Wien Klin Wochenschr* 91(4): 111-118; 1979.

Data on the association between estrogen therapy during menopause and the risk of endometrial carcinoma are reviewed. To date, animal studies and clinical observations indicate that estrogens should not be regarded as carcinogens that lead to the development of endometrial carcinoma. However, because of their proliferative action, they can promote the carcinogenicity of certain other agents in hormone-dependent tissues. Progestogens, on the other hand, are anti-proliferative and they impede the action of these agents. Retrospective studies recently published in the US have revived the question of whether the risk of carcinoma is increased by estrogen administration after menopause. The value of these studies is criticized on the grounds of methodological bias, diagnostic errors in the precancerous and early stages of endometrial carcinoma, and therapeutic protocols. In any event, estrogens should always be given cyclically and at the lowest possible doses. In women with known risk factors, estrogens should be combined with progestogens, as in a normal cycle. This two-phase therapy could constitute a generally applicable alternative to menopausal estrogen therapy in the future. (53 refs)

79-1826 Role of Estrogens in the Pathogenesis of Endometrial Adenocarcinoma. (Ita) Campagnoli, C. (II Clinica Ostetrica e Ginecologica, Universita di Torino, Turin, Italy); Chiara, G.; Gilli, V. *Minerva Med* 70(2): 97-111; 1979.

Studies of the role of estrogens in the pathogenesis of endometrial adenocarcinoma are reviewed. Hyperplasia and subsequent malignant transformation of the endometrium were observed in rabbits, mice, and rats during long-term estrogen treatment. Endometrial adenocarcinoma is most

likely to occur if long-term estrogen stimulation is not counterbalanced adequately by progesterone (unopposed estrogen action). In this sense, nulliparity, late menopause, obesity, polycystic ovaries, and hormone-producing ovarian tumors (ie, granulosa cell and theca cell tumors) are risk factors in endometrial adenocarcinoma. The low incidence of endometrial adenocarcinoma in Japanese women compared with Caucasians is believed to be due to a difference in hormonal homeostasis that is ascribable to environmental and dietary factors (lower fat and protein levels in the Japanese diet). (24 refs)

- 79-1827 Carcinogenic Hazards from Prenatal Exposure to Environmental Chemicals.** (Eng) Napalkov, N. P. (Petrov Res. Inst. Oncology, Leningrad, USSR). *Cancer Detect Prev* 2(1): 21-46; 1979.

Literature data on experimental transplacental carcinogenesis are reviewed. The most important finding from animal experiments is that exposure to even a single dose of a carcinogen during pregnancy can lead to tumor development in the offspring or to increased sensitivity of the offspring to subsequent exposure to carcinogens, with the effects being additive. A chemical may have a typical organotropic tumorigenic effect in adults that differs from that in offspring exposed in utero. The fetus is most sensitive to the carcinogenic effects of a chemical during the later periods of gestation, ie, the histogenesis stage; to its teratogenic effects during the organogenesis stage; and to its lethal effects during the early stages. Transplacental exposure to carcinogens can induce congenital defects and/or neoplastic growth in the offspring. These events are different consequences of the same exposure rather than subsequent stages of one process. The type of teratogenic and carcinogenic response depends on the species of the organism, the nature and dose of the chemical, and the stage of embryogenesis. The risk of tumor development in offspring exposed to a carcinogen in utero is also determined by passage of sufficient concentrations of a carcinogen or its active metabolites through the placental and embryonic membrane barrier. One of the characteristics of transplacental carcinogenesis is the frequent development of multiple primary tumors. Several observations in rats, hamsters, and mice are in agreement with the field origin theory of multicentric tumor growth; ie, an entire tissue system or a large portion of it is considered a single tumor field. (59 refs)

- 79-1828 Environmental Carcinogenesis.** (Eng) Hadden, J. W. (Dept. Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021). *Clin Bull* 8(3): 123-127; 1978.

Research efforts are outlined that were undertaken to determine what undiscovered carcinogenic materials present themselves to the human population, whether very small amounts of known, potent carcinogens in the environment

constitute a risk, which individuals are most susceptible to carcinogens, and what factors may influence this susceptibility. (no refs)

- 79-1829 The Workplace as a Cause of Cancer--Part II.** (Eng) Schottenfeld, D. (Epidemiology and Preventive Medicine Service, Dept. Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Haas, J. F. *Clin Bull* 8(3): 107-119; 1978.

The relevance of animal and in vitro studies for predicting human risks is reviewed. The results of animal and of clinical and epidemiologic studies of industrial agents associated with cancer are tabulated. The agents include federally regulated carcinogens and agents for which epidemiologic and/or animal studies suggest carcinogenic potential. Since it is difficult to determine the 'safe' level of human exposure to any suspect carcinogen with any degree of confidence, the concepts of 'acceptable risk' and 'risk-benefit analysis' are emerging in counterpoint to the issue of a 'risk-free' workplace. (110 refs)

- 79-1830 The "Beer Cancer".** (Ger) Oeser, H. (Kurfurstendamm 37, D-1000 Berlin 15, W. Germany). *Munch Med Wochenschr* 121(8): 256-257; 1979.

A recent newspaper report that beer is carcinogenic is criticized. The beer output in Germany has increased > 300% during 1950-1962. During 1962-1976, the period when an increased cancer mortality could be expected (allowing a latency of 15-20 yr), colon carcinoma has increased 30% and stomach carcinoma has decreased 30%. The total cancer mortality rate for men has increased slightly; if lung cancer is excluded, the rate has declined. (no refs)

- 79-1831 The Biological Effects of Ionizing Radiation.** (Eng) Barnett, M. H. (Div. Training and Medical Applications, Bureau Radiological Health, Food and Drug Admin., Dept. Health, Education, Welfare, Rockville, MD). *Conn Med* 43(2): 75-80; 1979.

The biological effects of ionizing radiation are described. The sequential pattern of these effects, short- and long-term effects, life-span shortening, and carcinogenic, embryological, and genetic aspects are discussed. There is evidence that some effects of radiation constitute nonthreshold phenomena. The occurrence of cancer in radium dial painters, radiologists and dentists, uranium miners, atomic bomb survivors, children irradiated in utero, and patients irradiated for ankylosing spondylitis, thymus enlargement, tinea capitis, and TB (pneumothorax induction) is summarized briefly. (9 refs)

79-1832 Radiation Effects on Pre-natal Development and Their Radiological Significance. (Eng)

Mole, R. H. (Medical Res. Council, Radiobiology Unit, Harwell, Didcot, Oxon OX11 0RD, England). *Br J Radiol* 52(614): 89-101; 1979.

The effects of irradiation from medical diagnostic procedures received during the first 4 mo of pregnancy are reviewed. The types of risk considered are death of the developing embryo, birth of a malformed child, and childhood cancer. The overall risk of serious radiation-induced harm following exposure of the embryo or fetus to diagnostic x-rays in the first trimester is most probably in the range 0-1 cases/1,000 women receiving 1 rad tissue dose. The 0-1 cases would mostly be childhood cancer. The natural expectation for the birth of a markedly handicapped child at the end of a normal pregnancy is 1/30. The risk from medical diagnostic procedures would seem to be at least 30 times smaller than this. A recent survey of clinical and experimental information on the developmental effects of irradiation in utero by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) is critically reviewed in an appendix. (29 refs)

79-1833 On the Mechanism of Film Neoplastogenesis.

(Eng) Libenson, L. (Western Pennsylvania Hosp., 4800 Friendship Ave., Pittsburgh, PA, 15224); Jena, M. *Med Hypotheses* 5(1): 67-82; 1979.

It is hypothesized that protracted low pH values produced in the cell environment might be both the cause and effect of the neoplastic transformation induced by implanted chemically inert films. The following sequence of changes is suggested. Hindrance of interstitial fluid circulation by the implanted film will induce anoxia and, hence, increased lactic acid production by the cells in the vicinity of the film. The protracted low pH produced by the lactic acid will increase the permeability of the capillaries and elicit high concentrations of plasma protein in the fluid near the film. The low pH will also tend to stimulate the pinocytotic uptake of protein-containing interstitial fluid by the cells. Continuous uptake and catheptic hydrolysis of plasma protein at the lower intrapinosomal pH and further hydrolysis of the formed polypeptides at neutrality or slightly alkaline pH will produce an overabundance of complementary amino acids that will be used to synthesize specific cell proteins and other constituents. The overabundance of nutrients will accelerate synthetic processes and promote cell growth and multiplication. Adaptation of normal cells to survive and multiply at low pH would take place concomitantly with their transformation into neoplastic cells. Deletion of enzymes sensitive to low pH would account for the tendency of the neoplastic cells to converge to a uniform enzymatic pattern regardless of the tissue of origin. (44 refs)

79-1834 Photoimmunology. (Eng) Morison, W. L. (Dept.

Dermatology, Massachusetts General Hosp., Boston, MA, 02114); Parrish, J. A.; Epstein, J. H. *Arch Dermatol* 115(3): 350-355; 1979.

Several aspects of photoimmunology, the study of the effects of nonionizing radiation on normal and abnormal immune function, are reviewed. In animals, the immune system appears to be centrally involved in experimental photocarcinogenesis, and some studies suggest that altered immune function may be a factor in the initiation and growth of UV light-induced neoplasms in humans. (96 refs)

79-1835 Genetics of Resistance of Animals to Viruses: I. Introduction and Studies in Mice. (Eng)

Bang, F. B. (Dept. Pathobiology, The Johns Hopkins Univ., Baltimore, MD). *Adv Virus Res* 23: 269-348; 1978.

Inherited resistance to animal viruses is reviewed. Hypotheses concerning host-virus interactions in plants, *Drosophila*, and other insects are presented, along with a description of the origin and development of inbred mice (mouse genetics). The genetic resistance of mice to arboviruses, mouse hepatitis virus, influenza and miscellaneous acute viral infections, scrapie, mouse leukemia virus, mouse mammary tumor virus, and other viruses causing chronic infections (lactic dehydrogenase virus, cytomegalovirus, polyoma virus, and viruses causing lymphocytic choriomeningitis and slow disease of the CNS) is discussed. For each virus or group of viruses, the following points are covered: measurement of the genetic compatibility of host and virus interaction; whether the inherited resistance follows the predictions of Mendelian ratios; the number of genes involved and the degree to which they are linked; cytoplasmic factors in the host that may modify the virus infection; the ontogeny of resistance in an individual animal; the cellular or tissue type involved in resistance; the ability of drugs or environment to modify genetic resistance; the possible existence of viral variants that overcome cellular genetic resistance; and whether a compatible pair of virus and host cells yield a one-hit curve of lesions. (259 refs)

79-1836 Generation of Diversity among Murine C-Type Viruses via Envelope Gene Recombination.

(Eng) Elder, J. H. (Dept. Cellular and Developmental Immunology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037); Gautsch, J. W.; Jensen, F. C.; Lerner, R. A. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 553-560; 1978.

Structural analyses of the surface glycoprotein gp70 of the murine C-type viruses that suggest that gp70 plays a central role in the generation of murine C-type virus diversity are reviewed. Tryptic fingerprint analysis of gp70 and the internal proteins p30 and p15 from representatives of the three

main endogenous virus groups (Akv-2 ecotropic virus, 1504A wild mouse amphotropic virus, and NZB xenotropic virus) indicated that p30 and p15 have only subtle group specificity. However, an extreme divergence was observed in the structure of the gp70's from these viruses. Structural analysis of the mink cell-focusing (MCF) virus isolates of AKR mice indicated that recombination between endogenous ecotropic and xenotropic viruses can occur within the envelope gene encoding gp70. This implies that the noncoordinate divergence of gp70 observed in the endogenous C-type viruses was the result of recombination within the envelope gene. In the high leukemia AKR mouse strain, lymphomas begin to develop at 6 mo of age. AKR ecotropic virus is produced throughout life and does not appear to be the direct causative agent in AKR leukemia. Xenotropic virus expression begins in the thymus at 4-6 mo of age, but xenotropic virus alone appears to have no oncogenic potential. MCF virus, however, is produced in the preleukemic and leukemic thymus and is not present in young AKR mice. Tryptic-peptide analysis showed specific homology with xenotropic virus in the gp70 of MCF-247, whereas chymotrypsin cleavage revealed peptides specific for AKR ecotropic virus gp70. The MCF viruses result, therefore, from an intragenic recombination between endogenous ecotropic and xenotropic viruses and may be the true causative agents of AKR lymphoma. (19 refs)

79-1837 Cellular Differentiation and Malignant Transformation. (Fre) Foa, C. (Unite 119, INSERM, boulevard Lei-Roure, F13009 Marseille, France); Nicoli, J.; Meyer, G. *Bull Cancer (Paris)* 66(1): 29-36; 1979.

Studies of cell differentiation and malignant transformation are reviewed with special regard to the development of melanomas and transformation by papovaviruses. Malignant transformation can represent a phenomenon independent of differentiation or it can represent a particular form of differentiation. Transformation by an oncogenic virus is linked with the coding of proteins by the virus genome; these proteins are differentiation inducers. Ultrastructural, cytoenzymatic, and cytogenetic studies of human malignant melanomas have demonstrated that accumulation of melanin and malignancy are often simultaneous, but that there are also melanocytes in which these two phenomena are dissociated; ie, there are highly malignant pigmented cell lines, malignant achromic cell lines, and malignant pigmented cell lines developing secondarily from a nonmalignant, apparently achromic stage. The highly malignant pigmented cells are believed to be melanocytes that have preserved the features of differentiation but have lost their regulation mechanism, whereas the achromic cells present in certain mixed tumors maintain their regulation mechanism and are capable of repressing melanin synthesis. (50 refs)

79-1838 Reptilia-related Viruses. (Eng) Lunger, P. D. (Univ. Delaware, Newark, DE); Clark, H. F.

Adv Virus Res 23: 159-204; 1978.

In-depth studies of reptilian virology are reviewed. The topics covered include DNA and RNA-containing viruses, intramitochondrial viruses, infection of reptilian cell cultures with nonreptilian viruses, interferon production by tortoise cells, and virus-induced reptilian cell transformation. (124 refs)

79-1839 Differentiation and Leukemic Transformation of Thymus-derived Lymphocytes. (Eng) Waksal, S. D. (Cancer Res. Center, Tufts Univ. Sch. Medicine, Boston, MA, 02111). *Cold Spring Harbor Conf Cell Prolif* Vol. 5(Book B), 994 pp.; 641-655; 1978.

Studies of the differentiation and leukemic transformation of thymus-derived lymphocytes are reviewed. A technique has been developed for the culture of thymus epithelium (TE) in monolayers devoid of any lymphocytic elements. Culture of spleen cells from congenitally athymic (nu/nu) mice with congenic TE monolayers resulted in the acquisition of Thy-1, a differentiation antigen associated with mature T lymphocytes, and the induction of helper T-lymphocyte activity. Studies of the responsiveness of prothymocytes and thymocytes to thymic hormone and TE using three types of cell populations as target cells showed that the target cells most reactive to the TE monolayers were least reactive to the hormone. The cells, therefore, lose reactivity to TE monolayers as they acquire reactivity to the hormone. TE derived from aged AKR mice directly initiated leukemic transformation of young AKR thymocytes in vitro, whereas control monolayers from young nonleukemic AKR mice had no such effect. Studies using thymectomized animals indicated that the donor thymocytes could manifest leukemia even in the absence of further differentiation in vivo. The TE cells from aged, but not young, nonleukemic AKR mice contained mink cell focusing virus, one of a new class of recombinant polytropic C-type RNA viruses (ie, both ecotropic and xenotropic host range). It is suggested that this new class of viruses is associated with leukemogenesis. (32 refs)

79-1840 Recent Advances in Polyoma Virus Research. (Eng) Consigli, R. A. (Div. Biology, Kansas State Univ., Manhattan, KS); Center, M. S. *CRC Crit Rev Microbiol* 6(3): 263-299; 1978.

Recent advances made in polyoma virus research, particularly those concerning polyoma infection of a permissive host, are reviewed. The virus genome has been dissected and has been shown to be almost completely saturated with genetic and biological markers. Information concerning the function of each gene product, together with the possible sequence of the viral DNA, will make polyoma and the closely related simian virus 40 the most completely understood of all animal viruses. The early region of the polyoma genome will proba-

bly be known in detail within the next few years. Recent studies have indicated that antiserum to large tumor (T) antigen reacts with a 100,000-dalton (100K) protein and also with a prominent 21K protein, which has been designated small t antigen. This protein may have common sequences with the 100K T-antigen polypeptide. The absence of this protein in cells infected by a mutant with a host range and transformation defect (NG18) suggests that it may be involved in the maintenance of transformation. The mechanism by which the 21K t antigen is made is unknown, but it has been proposed that early messenger RNA is modified such that it is translated to form more than one protein. Early messenger RNA may contain one or more regions that are looped out from the polynucleotide chain; the 100K T antigen may be made from sequences excluding the loop, but the 21K protein may be made from some sequences common to T antigen but also from those containing the loop. VP₃, a viral capsid protein, might play some role in maintaining certain phenotypic properties of the transformed cell. Other studies strongly suggest that the viral capsid protein VP₁ is initiated independently of VP₃. Polyoma virus has been useful and possibly has unlimited potential as a tool or biological probe for understanding host transcriptional and replicative processes. (229 refs)

- 79-1841 **Bovine Leukemia Virus.** (Jpn) Onuma, M. (Dept. Veterinary Medicine, Hokkaido Univ., Sapporo, Hokkaido, Japan 060). *Virus* 28(2): 53-60; 1978.

The morphology and biochemical structure of bovine leukemia virus (BLV), the surface antigens of the bovine lymphosarcoma cells, the method of BLV infectious transfer, and the relationship between sporadic bovine leukemia and BLV are reviewed. (97 refs)

- 79-1842 **Unit of Biological Carcinogenesis.** (Eng) Geser, A. (International Agency Res. Cancer, Lyon, France). *IARC Annual Report* 66-76; 1978.

The 1978 activities of the Unit of Biological Carcinogenesis of the International Agency for Research on Cancer are reported. Etiological studies of Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC) continued to be the main occupation of the Unit. The testing of 14 sera from Ugandan BL patients prior to tumor onset showed that anti-Epstein-Barr virus (EBV)/viral capsid antigen (VCA) activities were significantly increased in BL patients years before tumor appearance. In some cases, however, the EBV/VCA titers were not raised before BL, and the presence of the EBV genome could not be demonstrated. To establish whether a form of BL exists in Africa that is not EBV-associated and to support the serological findings, it was decided that BL detection in the child cohort bled in Uganda between 1972 and 1974 should be continued. The geographical association between the high incidence of malaria and BL is being investi-

gated in Uganda and Tanzania. The fact that BL patients in Uganda did not reveal a higher malaria burden prior to tumor development than controls does not favor the hypothesis that malaria causes BL. However, malaria parasitemia varies drastically daily in children in hyperendemic areas, and a single examination cannot be expected to give a significant difference between BL candidates and controls, even though such a difference may have existed. In Tanzania, sera will be collected from children in one region who are undergoing malaria prophylaxis and from children in another region where chloroquine is not being distributed. In Singapore approx 5,000 Chinese men will be bled and followed for 5 yr to see whether the EBV antibody profile in persons who subsequently develop NPC differs from that of people who do not. Seroepidemiologic and immunogenetic studies of Tunisians are also being conducted. (7 refs)

- 79-1843 **Hepatocellular Carcinoma and Hepatitis B Virus Markers in Europe and U.S.A. (2 Letters to Editor).** (Eng) Omata, M. (Univ. Southern California Liver Unit, John Wesley Hosp., Los Angeles, CA, 90007); Ashcava, M.; Peters, R. L.; Johnson, P. J. *Lancet* 1(8113): 433-434; 1979.

Comments on a paper suggesting a close relation between hepatitis B virus (HBV) infection and hepatocellular carcinoma (HCC) in Greek patients are presented. Although some aspects of the paper are questioned, one group of researchers found a close association between HBV infection and HCC in the US. Another researcher states that to demonstrate a causal relationship between HCC and HBV infection, it is necessary to show that proved noncirrhotic patients have a significantly higher incidence of HBV infection than matched controls or to show that patients dying with cirrhosis complicated by HCC have a higher incidence of HBV infection than those dying with cirrhosis alone. (12 refs)

- 79-1844 **On the Relationship Between Viral Hepatitis and Hepatocarcinoma.** (Eng) Pollice, L. (Inst. Pathological Anatomy, Univ. Bari, Bari, Italy). *Med Hypotheses* 5(2): 253-255; 1979.

Evidence suggesting a possible relationship between hepatitis B virus (HBV) infection and hepatocellular carcinoma (HCC) is reviewed. This evidence includes the observation of hepatitis B surface antigen (HBsAg) in the sera of noncirrhotic patients with HCC, the high incidence of HBsAg positivity among mothers of children with hepatoma, and the fact that hepatic oval cells are a good culture medium for HBV. These cells are also directly involved in α -fetoprotein production, which is markedly elevated in 80% of HCC patients. (21 refs)

- 79-1845 Immunological and Virological Aspects of Cervical Carcinoma.** (Eng) Hillemanns, H. G. (Universitäts-Frauenklinik, Hugstetterstrasse 55, D-7800 Freiburg im Breisgau, W. Germany); Sellin, D.; Petersen, E. E. In: *Cervical Pathology and Colposcopy. Selected Papers from the Second World Congress of Cervical Pathology and Colposcopy held in Graz, Austria, 15-18 October 1975.* Burghardt, E.; Holzer, E.; Jordan, J. A., eds. (Stuttgart: Georg Thieme Publishers): 146 pp.; 97-102; 1978.

Immunological and virological studies concerning cervical carcinoma are reviewed, with particular reference to the relationship between this neoplasm and herpes simplex virus type 2 infection. (17 refs)

- 79-1846 6. Interdisciplinary Programme and International Liaison Unit.** (Eng) Linsell, C. A. (International Agency Res. Cancer, Lyon, France). *IARC Annual Report* 121-131; 1978.

The 1978 activities of the Interdisciplinary Programme and International Liaison Unit of the International Agency for Research on Cancer are reported. Priority areas for cancer research in developing countries are identified, and progress in studies of cancer immunology, prenatal events and childhood cancer, liver cancer, and esophageal cancer is summarized. (8 refs)

- 79-1847 Immunodeficiency Diseases and Malignancy.** (Eng) Spector, B. D. (Dept. Lab. Medicine and Pathology, Univ. Minnesota, Minneapolis, MN, 55455); Good, R. A.; Kersey, J. H. In: *Gastrointestinal Tract Cancer.* Lipkin, M.; Good, R. A., eds. (New York, London: Plenum Medical Book Co.): Sloan Kettering Inst. Cancer Series 602 pp.; pp. 51-70; 1978.

This review of immunodeficiency (ID) diseases and malignancy is based on 205 reported cases of cancer occurring in patients with primary ID diseases. The ID diseases occurring in these patients included X-linked agammaglobulinemia (12 cases), IgA deficiency (13), IgM deficiency (7), variable ID (58), severe combined ID (11), ataxia-telangiectasia (70), and Wiskott-Aldrich syndrome (34). Each primary ID disease was associated with a significant number of lymphoreticular tumors, which accounted for 57% of all cancers and for the majority of cell types in 5/7 primary ID's. The distribution of cancers by age and primary site indirectly supports the conclusion that immunodeficient patients are at greatly-increased risk for developing cancer. The high male-female ratio (2:1) can be attributed to the X-linked disorders of childhood. Sex became a less significant variable beyond childhood. There was a surprisingly large number of gastrointestinal malignancies (26), particularly stomach cancers (18). Primary ID diseases likely provide a dramatic example of the influence of genetic factors on malignancy, since the lym-

phoid apparatus in individuals with these diseases is both the site of genetic aberration and the principal site of cancer development. Hypotheses of the mechanisms of lymphoid system oncogenesis fall into at least two categories: (1) the immune system in primary ID's is subject to the formation of too many malignant cells; and (2) the immune system in these diseases has a decreased ability to recognize and destroy malignant cells. Pathogenic mechanisms that may be responsible for the increased transformation of lymphoid cells include intrinsic defects in lymphoid cells, chronic antigenic stimulation, the activation of endogenous viruses or infection with exogenous oncogenic viruses, and the lack of regulatory feedback mechanisms, which results in enhanced lymphoid proliferation. (74 refs)

- 79-1848 The Structure of H-2 Antigens and Their Role in Tumor Cell Recognition.** (Eng) Cunningham, B. A. (Dept. Developmental and Molecular Biology, Rockefeller Univ., New York, NY, 10021); Milner, R. J.; Schrader, J. W.; Reske, K.; Henning, R.; Ziffer, J. A.; Edelman, G. M. *30th Ann Symp Cancer Res* 163-176; 1978.

The structure of the major histocompatibility (H-2) antigens of the mouse and their role in the lysis of tumor cells and virally infected cells by cytotoxic T lymphocytes are reviewed. The genes for the H-2 antigens are located in two closely linked loci (H-2K and H-2D) on the 17th chromosome and are characterized by extensive polymorphism. Between these loci are two other regions: the I region contains immune response genes and the S region contains genes specifying a serum protein and its sex-linked variant. These data suggest that the H-2 complex contains a variety of genes that arose by duplication. In addition, two regions, T1a and the t-complex, which are outside the H-2 complex but are on the 17th chromosome, may have similar properties with regard to the immune system. The sequences and amino acid compositions of the β -microglobulin of several species indicate that it is a highly conserved protein. No variant has been detected within a species by serological techniques or by amino acid sequence analysis. The most striking feature of the human protein is its similarity to the constant homology regions of all immunoglobulins, indicating that they probably share a common evolutionary origin. The amino acid sequences and products of the H-2K and H-2D alleles are also similar, suggesting that these two regions arose by duplication of an ancestral gene. The similarity between H-2 and the human major histocompatibility (HLA) antigen sequences also supports the conclusion that these two systems serve the same function. H-2 antigens are intimately involved in the lysis of virally infected and tumor cells by cytotoxic T cells. Thus, it is likely that the cytotoxic T cell has a single receptor and the H-2 molecule is part of or directly affects a single component on the target cell, or the cytotoxic cell has two separate receptors that recognize the target antigen and the H-2 molecule independently. Present evidence favors the first model. (44 refs)

- 79-1849 Transplantation in Nature.** (Eng) Beer, A. E. (Univ. Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, TX, 75235); Billingham, R. E. *Perspect Biol Med* 22(2, part 2): 155-169; 1979.

An account of certain exceptional situations in nature in which successful allotransplantation occurs is presented. Topics discussed include parabiotic unions in deep-sea angler fish, synchorial twinning in cattle, a venereally transmissible tumor in dogs, maternal-to-fetal transmission of malignant melanoma in humans, mammalian reproduction and transplantation, deportation of trophoblasts, choriocarcinoma, maternally induced runt disease, and suckling as a possible form of transplantation. (22 refs)

- 79-1850 Polypeptides Regulating Lymphocyte Differentiation.** (Eng) Goldstein, G. (Ortho Pharmaceutical Corp., Raritan, NJ, 08869). *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book A), 528 pp.; 455-465; 1978.

The isolation, chemical structure, site of production, and actions of several polypeptides associated with the regulation of lymphocyte differentiation are reported. Thymopoietin, which is synthesized and secreted by epithelial cells of the thymus, induced the differentiation of prothymocytes to thymocytes in vitro and in vivo. Thymopoietin induction of prothymocyte-to-thymocyte differentiation is mediated by a cAMP second signal. Thymopoietin also affects a number of tissues, including T cells, B cells, macrophages, granulocytes, and the neuromuscular junction, suggesting that it also functions as a hormone. These actions appeared to be mediated by cyclic guanosine monophosphate as a second signal. Ubiquitin has been found in all mammalian tissues and does not appear to be implicated as a physiological regulatory molecule for lymphocyte differentiation; it may function as a structural or controlling element related to DNA. Another peptide, termed the Bach nonapeptide, is a circulating peptide with potent actions on lymphocyte differentiation, but its source of production and circulating levels are not yet known. Bursopoietin is a short peptide purified from chicken bursa of Fabricius. Preliminary studies have demonstrated that it has a B-cell-differentiating activity. It is concluded that thymopoietin, bursopoietin, and perhaps the Bach nonapeptide induce the differentiation of committed early precursor cells and possibly regulate the activities of differentiated cells in a hormonal rather than in an inductive sense. (39 refs)

- 79-1851 Regulatory Interactions in Normal and Leukemic Myelopoiesis.** (Eng) Moore, M. A. (Sloan-Kettering Inst. Cancer Res., New York, NY, 10021); Kurland, J.; Broxmeyer, H. E. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book A), 528 pp.; 393-404; 1978.

Functional and regulatory characterization of leukemic cell

lines derived from in vivo tumors or from tumors that developed spontaneously in in vitro continuous bone-marrow culture is discussed. Constitutive production of colony-stimulating factor (CSF) characterized cultures of murine peritoneal macrophages, and it could be increased by the addition of lipopolysaccharide (LPS). Macrophages generated from bone marrow-derived granulocyte-macrophage committed stem cells (colony-forming unit--culture, CFU-C) and 3/4 neoplastic monocyte or macrophage cell lines were not constitutive CSF producers but were capable of production following LPS stimulation. In vitro activation of normal peritoneal macrophages and in vitro-generated macrophages with LPS produced a 10-fold and 5-fold increase in prostaglandin E (PGE) production, respectively. A similar linkage between induction of CSF and subsequent synthesis of PGE was observed in the monocyte-macrophage cell lines. Production of PGE by normal or neoplastic B or T lymphocytes was not observed. Spontaneous transformations observed in allogeneic continuous bone-marrow cultures were characterized by an increased rate of cell production, development of agar cloning capacity in the absence of CSF, and failure of the cells to mature. These events were paralleled by marked aneuploidy, capacity of the cell to grow continuously in the absence of an adherent marrow cell population, and tumorigenic potential in nude mice or normal mice syngeneic with the second marrow cell population. Transformation was also observed in syngeneic cultures of CBA bone marrow plus fetal liver cells. These models of spontaneous in vitro leukemogenesis may reflect events associated with natural leukemogenesis more accurately than transformation systems involving infection with murine leukemia viruses. (22 refs)

- 79-1852 Plasmacytomagenesis and the Differentiation of Immunoglobulin-producing Cells.** (Eng) Potter, M. (Lab. Cell Biology, NCI, Bethesda, MD, 20014); Cancro, M. *30th Ann Symp Cancer Res* 145-161; 1978.

The relationship between plasmacytomagenesis and the differentiation of immunoglobulin (Ig)-producing cells is reviewed. Evidence is presented that suggests that the progenitors of plasmacytomas in the BALB/c mouse system are derived from a relatively specific subpopulation of B lymphocytes that are generally in a comparatively late stage of differentiation. IgA-producing cells are implicated as the progenitor subpopulation. These cells probably originate as rarely occurring members of the B-lymphocyte subpopulation that lack or escape normal regulatory constraints with respect to their proliferative capacity. They then attain clonal sizes that emerge as detectable plasmacytomas through interactions with unusual, perhaps selective, microenvironmental influences that enhance their expansion and survival. The inbred-strain susceptibility implicates germ-line genes as playing a role in BALB/c plasmacytomagenesis. The effect of the gene(s) may only be to increase the probability of neoplastic change, however, and may not be the sole determinant. Other mutational events (somatic mutations, C-type RNA virus production) may complement germ-line genes

that govern susceptibility. A powerful influence in plasmacytomagenesis is the promoting effect of the oil granuloma, which may also act as a selecting factor that favors the growth of potential or preplasmacytoma cells. (68 refs)

- 79-1853 Ocular Tumor Immunology.** (Eng) Char, D. H. (Dept. Ophthalmology, Francis I. Proctor Foundation, Univ. California, San Francisco, CA). *Current Ophthalmology*: 74-100; 1978.

Several clinical and laboratory observations are consistent with the hypothesis that immunologic factors may be important in ocular malignancy. The possible role of the immune system in the host-tumor interaction is reviewed, and possible diagnostic and prognostic immunologic tests are presented. (93 refs)

- 79-1854 Bacterial Metabolism and Colon Cancer.** (Eng) Hill, M. J. (Bacterial Metabolism Res. Lab., Central Public Health Lab., Colindale Ave., London NW9 5HT, England). *Nutr and Cancer* 1(2): 46-50; 1979.

There are several possible substrates for carcinogen production by intestinal bacterial flora from dietary meat. Fecal tryptophan concentrations are much higher in large bowel cancer (LBC) patients than in controls, and in a study of six populations there was a relation between fecal tryptophan concentration and the incidence of LBC. The concentration increased with increased dietary protein. Methionine can be converted to ethionine, which is carcinogenic in rats, in the presence of sulfate ions by several bacteria. Lysine, arginine, ornithine, and lecithin are metabolized by the gut flora to cyclic secondary amines that are N-nitrosatable in the presence of nitrate. However, if the production of N-nitrosamine by bacterial action in the colon were important in large bowel carcinogenesis, the disease should be associated geographically with high levels of dietary nitrate. In fact, this is not so. Evidence linking cholesterol and/or its metabolites with colon cancer is contradictory. Fecal bile acid concentration is related to the amount of dietary fat. There is much evidence incriminating fecal bile acid metabolites in LBC. The fecal concentration of deoxycholic acid correlated well with the incidence of LBC in nine populations, but it was no better than total fecal bile acids as a discriminant in a case-control study. The results of this study are compatible with the postulate that the cocarcinogen causing LBC is an unsaturated bile acid, perhaps a 4,6-dien-3-one, produced by certain Clostridia from colonic bile acids. (35 refs)

- 79-1855 Recognitive Immunity in Colon Cancer.** (Eng) Berlinger, N. T. (Memorial Sloan-Kettering Cancer Center, New York, NY, 10021). In: *Gastrointestinal Tract Cancer*. Lipkin, M.; Good, R. A., eds. (New York,

London: Plenum Medical Book Co.): Sloan Kettering Inst. Cancer Series 602 pp.; pp. 71-92; 1978.

Evidence supporting the antigenicity of colon carcinomas, tests of recognitive immunity in the colon carcinoma patient, and escape mechanisms by which tumors continue to grow in patients who have demonstrated immune reactivity to tumor cells in vitro are reviewed. The antigenicity of colon carcinomas has been suggested by the results of serological studies, delayed hypersensitivity skin testing, and in vitro studies; the apparent specificity of colon carcinoma antigens; and evidence that the colon carcinoma antigen behaves like a true immunogenic substance. Diverse tests of recognitive immune function to various stimuli have been developed; if the patient is hyporesponsive in this regard, it may be logical to consider his tumor defense mechanisms to be deficient. Morphological tests of recognitive immune function involve determining the degree of lymphocytic infiltration of tumors and the lymph node histology. Another test of cellular immune function involves measuring the ability to mount a cutaneous delayed hypersensitivity reaction to intradermally injected, commonly encountered antigens. A third test is the mixed leukocyte assay. One reason that tumors continue to grow in patients who have demonstrated immune reactivity to tumor cells is that cells of certain tumors may be only weakly antigenic and may not provide a strong enough stimulus to provoke optimal recognitive and effector responses. Alternatively, the infrequent antitumor immunoreactivity observed in cases of poorly differentiated tumors may be due to the fact that these tumors are more widely spread and are, by some unknown mechanism, leading to immunological paralysis. A role for antibody has also been postulated in the mechanism by which tumors escape immune attack. (110 refs)

- 79-1856 Effects of Anaesthesia and Surgery on Immune Status.** (Eng) Walton, B. (Dept. Anaesthetics, London Hosp., London E1 1BB, England). *Br J Anaesth* 51(1): 37-43; 1979.

Evidence that exposure to anesthesia + surgery (A+S) alters many facets of immunocompetence is reviewed, particularly the possible clinical implications for anesthetic practice. A+S may alter immunocompetence by depressing a variety of both nonspecific resistance mechanisms and specific immune responses. In general, the hormonal aspects of the stress of A+S are more important with regard to immunosuppression after operation and possible development of malignancy than anesthetic regimes per se, the effects of which are short-lived. (103 refs)

- 79-1857 Cancer: The Survival of the Fittest.** (Eng) Markert, C. L. (Dept. Biology, Yale Univ., New Haven, CT, 06520). *30th Ann Symp Cancer Res* 9-22; 1978.

Neoplasias are defined as diseases of cell differentiation stemming from a misprogramming of normal gene function. This misprogramming can have many causes, but all cancer must act by changing the function of regulatory DNA. Ultimately, it is the pattern of gene activity that defines each kind of differentiated cell and each kind of neoplastic cell. With respect to rate of cell division, metastasis, and patterns of metabolism, neoplastic cells resemble some types of normal cells. They out-compete normal cells for ecological space, for the requirements for survival and reproduction. It is likely that several events, at least some of them possibly mutations, must accumulate in a cell before it becomes neoplastic. It is also likely that the frequency of neoplasias is reduced by the presence of such a tight, interdependent cellular organization that almost every aberrant step by any cell would prove fatal to that cell or prevent proliferation. The immune system is probably not very important in combating cancer. Neoplastic agents, including carcinogenic chemicals, physiological stress, and oncogenic viruses, probably all act by altering the regulatory DNA of the host cell genome so as to reprogram gene function in a neoplastic pattern. Inherited teratogenic development may be a nonmalignant expression of the same general kind of misprogrammed gene function stemming from changes in the regulatory DNA at critical stages in embryonic development. (41 refs)

- 79-1858 Neoplasms as Caricatures of Tissue Renewal.** (Eng) Pierce, G. B. (Dept. Pathology, Univ. Colorado Medical Center, Denver, CO, 80262); Cox, W. F. *30th Ann Symp Cancer Res* 57-66; 1979.

Study of tumor development has led to the concept that tumors are caricatures of the renewal process in normal tissues. Embryoid bodies derived from mouse teratocarcinomas and transplanted sc into mice gave rise to teratocarcinomas containing 12 or 15 somatic tissues characteristic of the tumors. It was concluded that embryonal carcinoma cells are the multipotential stem cells of teratocarcinomas capable of differentiating into functional and benign cells. These cells are also capable of participating in normal development evolving normal animals. Whereas teratocarcinomas are considered caricatures of embryogenesis, squamous cell carcinomas and adenocarcinomas of the breast are considered to be caricatures of tissue genesis. The target in carcinogenesis is probably an undifferentiated cell. The observation that normal and neoplastic stem cells are similar in their degree of differentiation sheds new light on the relationship of benign and malignant tumors. When chemical carcinogens are applied to the skin of an animal, benign tumors appear first, followed much later by the appearance of malignant tumors. This has led to the concept that the state of differentiation of the responding cell could determine the state of differentiation of the neoplastic stem cells derived from it and the order of appearance of tumors would depend on how well the neoplastic stem cell could respond to the environment in which it found itself. The long latent period in carcinogenesis may be due to the

growth-controlling effect of the normal environment on undifferentiated malignant stem cells. (22 refs)

- 79-1859 Quality Assurance for Pathology in Rodent Carcinogenesis Tests.** (Eng) Ward, J. M. (Carcinogenesis Testing Program, NCI, NIH, Del Ray 402, Bethesda, MD, 20014); Goodman, D. G.; Griesemer, R. A.; Hardisty, J. F.; Schueler, R. L.; Squire, R. A.; Strandberg, J. D. *J Environ Pathol & Toxicol* 2(2): 371-378; 1978.

The pathology methods and quality control procedures recommended and utilized by the National Cancer Institute Carcinogenesis Testing Program are reviewed. The necropsy examination involves systematic inspection of external and internal organs and tissues so that tumors and lesions can be detected prior to microscopic examination. Fixation, trimming, dehydration, embedding in paraffin, and sectioning of tissues should be performed by a pathologist or qualified technician, and the histopathologic examination should be performed by a pathologist. One pathologist evaluates all slides from all animals of the same species in each study. A quality assurance unit is recommended for assessing diagnoses and procedures in large-scale programs involving many pathologists from different laboratories. After review by this unit, the original pathologist is notified of important disagreements with his diagnoses and differences of opinion may be reconciled. The use of a computer-based system for recording diagnoses in a large study is desirable. The final report should be a concise and accurate reflection of the findings in both control and treated animals. (13 refs)

- 79-1860 Cytoskeletal Changes in Cell Transformation to Malignancy.** (Eng) Brinkley, B. R. (Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030); Miller, C. L.; Fuseler, J. W.; Pepper, D. A.; Wible, L. J. *30th Ann Symp Cancer Res* 419-450; 1978.

The structure, assembly, and distribution of microtubules and microfilament in normal and transformed cells are reviewed. In normal cells, the microtubules are arranged in an elaborate complex throughout the cytoplasm. This cytoplasmic microtubule complex (CMTC) is disassembled at the beginning of mitosis and is replaced by a mitotic apparatus that segregates the chromosomes during mitosis. When mitosis is completed, the CMTC reappears in each daughter cell. Bundles of microfilament actin "stress fibers" also appear in the cytoplasm. They behave similarly to the microtubules during the cell cycle, and both structures seem to be involved in maintaining the cell shape. The major microtubule-organizing center appears to be in the centrosphere region of the cell containing the centrioles and associated organelles. The cytoplasmic microtubules are disassembled by colcemid, chilling to 0-4 C, ionophore A23187 + elevated Ca (4.7 mM), local anesthetics, trypsin, neuraminidase, and, to a lesser extent, cytochalasin B. The CMTC becomes more organized in the

presence of cyclic nucleotides. The cytoplasmic microtubules and microfilaments are reduced in number and more randomly oriented in transformed cells. There is an apparent correlation between the acquisition of anchorage-independent growth in vitro and the diminution of cytoskeletal elements. (72 refs)

- 79-1861 Cell Differentiation and Cancer--A Summary.** (Eng) Paul, J. (Beatson Inst. Cancer Res., Wolfson Lab. Molecular Pathology, Bearsden, Glasgow G61 1BD, Scotland). *30th Ann Symp Cancer Res* 525-532; 1978.

Highlights of papers presented at a symposium on cell differentiation and cancer are summarized. Cancer is essentially an environmental disease, which suggests that the basic lesion may be mutation. With regard to systems that neutralize the effects of mutations, the concepts of immune surveillance and the existence of highly efficient DNA repair mechanisms in multicellular creatures are not supported by the available evidence. It is more likely that the developing organism has a mechanism for selecting against abnormal cells. The fact that normal mice can be derived from teratocarcinoma cells demonstrates that normal tissues can be derived from tumor cells. Furthermore, different kinds of cancers can derive directly from stem cells; the transformed cell of leukemia may actually be a stem cell in one of the late transit populations. Many tumors can revert to more normal tissue by differentiation. common quantitative differences that are characteristic of tumor cells can be exploited in the diagnosis and management of cancer. Finally, there is some doubt that a round of DNA replication is necessary for the process of commitment to differentiation. (8 refs)

- 79-1862 Selectivity and Rejectivity in Cancer Metastasis.** (Eng) Onuigbo, W. I. (Dept. Histopathology, Teaching Hosp., Enugu, Nigeria). *Med Hypotheses* 5(1): 185-191; 1979.

The concepts of selectivity and rejectivity are discussed in relation to cancer metastasis. Selectivity denotes the formation of a secondary tumor in an organ such that its localization pattern is peculiar. The opposite phenomenon is termed rejectivity. In humans, carcinomas appear to spread selectively to the umbilicus, whereas lymphomas seem to reject that site. All carcinomas do not show the same degree of selectivity for the umbilicus. In descending order, most umbilical metastases arise from the stomach, ovary, large bowel, pancreas, gallbladder, uterus, liver, and small bowel. It also appears that lymphomas are likely to show some differences with reference to rejectivity. Although as many as 128 cases of carcinoma of the umbilicus were recorded at the Mayo Clinic over the period 1950-1974, specific mention was not made of the absence of lymphomas in that series. It is suggested that prospective series should encompass both carcinomas and lymphomas. (41 refs)

- 79-1863 Proliferative Homeostasis and Its Age-related Aberrations.** (Eng) Martin, G. M. (Dept. Pathology, Univ. Washington, Seattle, WA, 98195). *Mech Ageing Dev* 9(5/6): 385-391; 1979.

The altered proliferative homeostasis that occurs in aging tissues often leads to multifocal proliferations or hyperplasias. The most important consequence of this age-related hyperplasia is that it could set the stage for tumor promotion--the second stage of the classical two-stage mechanism of chemical carcinogenesis. (45 refs)

- 79-1864 Developmental Genetics of Neural Tumors in Man.** (Eng) Knudson, A. G. (Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA, 19111); Meadows, A. T. *30th Ann Symp Cancer Res* 83-92; 1978.

The developmental specificities of the genes responsible for familial cases of CNS tumors are reviewed. Oncogenesis in cases of retinoblastoma, 40% of which are heritable in a dominant fashion, has been viewed as a two-step (mutation) process. In the hereditary form, one step is inherited and the other is somatic; in the nonhereditary form, both steps are somatic. Some cases of neuroblastoma and the more mature benign tumor ganglioneuroma are also attributable to a dominant gene that demonstrates considerable specificity. Over 20% of the cases of pheochromocytoma, a benign tumor that is not associated with neuroblastoma or ganglioneuroma, are apparently associated with a highly specific dominant gene. Specific dominant genes also appear to predispose to glioma and medulloblastoma, whereas the dominant gene for neurofibromatosis demonstrates less specificity and predisposes to an array of neural tumors. It is concluded that the normal alleles of neural tumor genes perform crucial functions in the development of the CNS. (31 refs)

- 79-1865 B-Lymphocyte Development and Growth Regulation.** (Eng) Melchers, F. (Basel Inst. Immunology, Basel, Switzerland). *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book A), 528 pp.; 485-503; 1978.

Studies of the development and growth regulation of B lymphocytes are reviewed. Studies using fetal mouse liver indicated that precursor B cells can divide in vitro under appropriate culture conditions, that this division is independent of exogenously added mitogen (lipopolysaccharide, LPS), and that these dividing precursors do not secrete immunoglobulin (Ig) to the extent that it could be monitored by a plaque. At the stage of differentiation at which B cells become surface Ig-positive and mitogen-sensitive, they fall into a resting state in which they do not synthesize DNA, do not divide, and appear small in size. One of the earliest changes detected in small B cells after mitogenic stimulation is the induction of IgM secretion, which precedes DNA synthesis within the cell cycle. The ratios of the rates of IgM synthesis over those of

all proteins made in the cell increase with increasing time of stimulation. Clonal analysis of B-cell growth indicates that B cells can balance within the cell cycle between growth and maturation to IgM secretion. An apparent difference demonstrated in reactivity to anti-Ig antibodies and the subsequent mitogenic stimulation of more immature (bone marrow) and mature (adult spleen) B cells may suggest that the proposed complexes of Ig molecules and mitogen receptors exist in different conformations in these two types of B cells. Inhibition of maturation to Ig secretion but not of growth by anti-Ig antibodies of mature splenic B cells stimulated by LPS also suggests that a balance between growth and maturation exists within the cell cycle of growing B cells. (48 refs)

79-1866 Nonrandom Involvement of Chromosomal Segments in Human Hematologic Malignancies.

(Eng) Rowley, J. D. (Dept. Medicine, Univ. Chicago, Chicago, IL, 60637). *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 709-722; 1978.

Studies of chromosome patterns in leukemia are reviewed, and the question of how and why nonrandom changes occur is considered. The first consistent chromosome abnormality identified in a human cancer was the Philadelphia (Ph¹) chromosome in leukemic cells from patients with chronic myelogenous leukemia (CML). The Ph¹ chromosome represents a translocation involving chromosomes 9 and 22. The 9:22 translocation was identified in 529/569 Ph¹ CML patients examined with banding techniques. In 100/135 CML patients in the terminal acute phase, additional chromosomal abnormalities were superimposed on the Ph¹ chromosome. In patients with acute nonlymphocytic leukemia, the most frequently observed chromosomal changes were a gain of number 8 and a loss of number 7. In patients with acute myeloblastic leukemia, a translocation involving numbers 8 and 21 was seen in 10%-15% of all patients with aneuploidy and it was frequently associated with the loss of a sex chromosome. Another consistent abnormality, a 15:17 translocation, was identified in acute promyelocytic leukemia. Studies of patients with hematological disorders who were trisomic for all or part of chromosome 1 have identified a specific region of chromosome 1 that is invariably present in the trisomic state in patients who have an excess of any part of 1. The mechanism for the production of specific, consistent reciprocal translocations is unknown. Preliminary studies of chromosome-gene correlations suggest that nonrandom chromosome aberrations change the level of some enzymes related to nucleic acid metabolism and that they may be an important component in the proliferative advantage of mutant cells in neoplasia. (35 refs)

79-1867 Regulation of Normal Cell Differentiation and Malignancy in Myeloid Leukemia. (Eng) Sachs,

L. (Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel). *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book

A), 528 pp.; 411-423; 1978.

Studies of the regulation of normal cell differentiation and malignancy in myeloid leukemia are reviewed. Normal myeloid precursors can be induced to differentiate to mature macrophages and granulocytes by the protein inducer MGI (macrophage and granulocyte inducer). One type of myeloid leukemic cell in humans (MGI+D+) can be induced to differentiate normally both in vitro and in vivo by MGI. The mature cells induced from MGI+D+ leukemic cells were no longer malignant in vivo and no longer multiplied in vitro. Both normal cells and MGI+D+ leukemic cells were induced by MGI to produce the same mature cells, and the process of differentiation occurred in the same sequence. The MGI+D+ leukemic cells were viable and could grow in the absence of MGI, whereas the normal cells required MGI for cell viability and growth. The change in requirement for MGI for cell viability was associated with a chromosome abnormality, which suggests a genetic origin for this leukemia. Once the change in requirement for MGI occurred, many other markers were induced that could be used for the genetic dissection of the controls for normal differentiation in these cells. Differences in competence for induction of normal differentiation in myeloid leukemic cells by MGI were associated with membrane differences between MGI+D+ and the less competent cells. Karyotype analysis has shown that the genes that control cell competence are located on mouse chromosomes 2 and 12 and that inducibility by MGI is controlled by the balance between these genes. Some of the stages of differentiation could be induced by certain steroids, but MGI is the only compound tested that induced all the changes to mature macrophages and granulocytes. Certain clones of leukemic cells could be induced by lipopolysaccharides to produce their own MGI. (59 refs)

79-1868 Interrelationship of Differentiation and Proliferation Control in Hemopoietic Stem Cells.

(Eng) Lajtha, L. G. (Paterson Labs., Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England); Lord, B. I.; Dexter, T. M.; Wright, E. G.; Allen, T. D. *30th Ann Symp Cancer Res* 179-193; 1978.

Proliferation control of hemopoietic stem cells operates at two levels: control of the 10-12 amplifying divisions during the transient life of the differentiated and maturing 'transit populations' and control of the steady-state maintenance of the stem cells. Regarding the transit populations, evidence exists for an apparent cell-line-specific feedback proliferation control in granulocytic, erythroid, and lymphocytic cells. Maintenance of stem cells in the noncycling G₀ state appears to be under the 'local' control of the spleen or bone marrow and dependent on local stem cell concentration. This local maintenance can be overridden by direct stimulation of the effective pathways of cell proliferation or by more physiological feedback information following depopulation of, for example, committed descendant cell populations. Stem cell inhibitors and stimulators can be used in combination to

manipulate the cycling of the stem cells, and they might have a role in manipulation of the drug sensitivity and recovery rate of hemopoietic cells during chemotherapy. A long-term bone marrow culture system has been developed in which stem cell maintenance and differentiation can be maintained for several weeks. The same method applied to human bone marrow might be useful for the study of human pluripotent stem cells. (42 refs)

79-1869 Regulation of Proliferation and Maturation at Early and Late Stages of Erythroid Differentiation. (Eng) Iscove, N. N. (Basel Inst. Immunology, CH4058 Basel, Switzerland). *30th Ann Symp Cancer Res* 195-209; 1978.

Regulation of the proliferation and maturation of RBC's from multipotential stem cells (MSC) to proerythroblasts is discussed. The initial event is the transition from MSC to cells that have lost the capacity for granulocyte-macrophage differentiation while retaining the potential for erythroid and megakaryocytic differentiation. These cells remain similar to the parent stem cells in size, density, low proliferative activity in the steady state, and responsiveness to regulatory influences in vivo. The next stage covers a spectrum characterized by the gradual onset of sensitivity to high concentrations of erythropoietin. The cells increase their proliferative capacity and become increasingly dependent on erythropoietin for maintenance of this capacity. Transition through this stage is influenced by an environmental cue related to the *s/l* gene product. Erythroid colony-forming units represent the final stage in the series. Their formation can take up to 8-12 days. They are larger and denser than the earliest cells, are highly erythropoietin-sensitive, and exhibit max proliferation. In the absence of erythropoietin, they lose their ability to respond to it when re-exposed. This stage precedes the onset of Hb synthesis by 24-30 hr. (31 refs)

79-1870 Bone Morphodifferentiation and Tumorigenesis. (Eng) Urist, M. R. (Bone Res. Lab., Univ. California, 1000 Veteran Ave., Los Angeles, CA, 90024). *Perspect Biol Med* 22(2, part 2): S89-S113; 1979.

Current knowledge of bone morphodifferentiation and tumorigenesis is reviewed. Bone morphogenesis is the process of controlled growth and development of bone tissue with the normal complement of bone marrow, whereas bone tumorigenesis is the process of uncontrolled bone cell growth without the normal complement of bone marrow. Methods have been devised for identifying and measuring the products but not the initiating agents of differentiation. The expectations are that quantitation of cell products will lend some clues as to the initiating agents or causal conditions. Experiments on nontumorous and tumorous bone suggest that extracellular matrix products include a bone morphogenetic protein, but only normal and not transformed cells are able to respond

to it. The development of the bone tissue cell types--mesenchymal cells, preosteoblasts, osteoblasts, and osteocytes--stops at the osteoblast stage. In Dunn osteosarcomas, transformed osteoblasts may replicate at a rate that is as much as 10 times that of preosteoblasts of even a rapidly developing fetus, but they fail to develop into mature osteocytes. It is not known why this is so. Normally, osteoblasts do not undergo mitotic division. Abnormally, the process of uncontrolled replication of osteoblasts establishes an antithetical relationship of bone morphogenesis and tumorigenesis. It appears that a combination of genetic, cytological, and local environmental agents is involved in bone tumorigenesis. (37 refs)

79-1871 The Precursors of Cutaneous Squamous Cell Carcinoma. (Eng) Brownstein, M. H. (Lab. Dermatopathology, Great Neck, NY, 11022); Rabinowitz, A. D. *Int J Dermatol* 18(1): 1-16; 1979.

Data on the cause, incidence, and histology of several precursors of squamous cell (epidermoid) carcinoma (scc) are reviewed. Cellular atypia (dysplasia) is present in premalignant lesions such as solar keratosis and Bowen's disease, and it is an indication that invasive scc may eventuate. Premalignancy is recognized microscopically as a disturbance of normal epidermal maturation, including loss of polarity, variation in shape and size of cells, nuclear hyperchromatism, prominent nucleoli, and abnormal mitotic figures. Although precursors of scc may have a wide variety of causes, histologically, they display only two basic patterns: bowenoid (in Bowen's disease; erythroplasia of Queyrat; intraepidermal epithelioma; bowenoid solar, arsenical, and radiation keratosis; leukoplakia; and base of cutaneous horn) and solar keratosis-like (in solar, arsenical and radiation keratosis; leukoplakia; and cutaneous horn). Carcinoma in situ, or intraepidermal carcinoma, is an advanced premalignant lesion with marked cellular pleomorphism in which the entire thickness of the epidermis may show the cytologic features of malignancy. Even though the morphologic criteria of malignancy may be satisfied, the term premalignant is used to indicate that, in a biologic sense, invasive malignancy has not yet occurred. Invasive scc sometimes develops at the site of a previous benign condition. In dermatoses such as lichen sclerosus et atrophicus of the vulva and epidermolysis bullosa, cellular atypia is not seen in the early stages; in some patients, however, cellular atypia and invasive malignancy develop later. (79 refs)

79-1872 Glomus Tumor of the Middle Ear: Origin, Symptomatology, and Treatment. (Eng) Bratt, G. W. (Div. Hearing and Speech Sciences, Vanderbilt Univ. Sch. Medicine, 1114 19th Ave. South, Nashville, TN, 37212); Bess, F. H.; Miller, G. W.; Glasscock, M. E. *J Speech Hear Disord* 44(1): 121-134; 1979.

The origin, symptomatology, and treatment of glomus tumor (GT) are reviewed. GT is histologically similar to the glomus jugulare body from which it arises; it is a blood vessel tumor with interspersed epithelioid cells. Unlike the glomus jugulare body, the tumor is much more common in women than in men. The incidence of GT, like that of the glomus body, is most prevalent in middle age and is rare in preadolescence. A review of 40 cases of GT (20 glomus tympanicum and 20 glomus jugulare) revealed that 38 of the tumors occurred in women. The mean age of the patients was 50.6 yr. The most prevalent clinical symptoms in both jugulare and tympanicum tumors were tinnitus and hearing loss. Although the prevalence of symptoms between the two types of glomus tumors was generally similar, two significant dissimilarities were noted. First, the incidence of early dizziness was higher in the tympanicum group than in the jugulare group. Secondly, although the incidence of hoarseness in the total population was low, hoarseness was associated only with the jugulare tumor. (42 refs)

79-1873 Induction of Pancreatic Tumors in Syrian Golden Hamsters (Meeting Abstract). (Eng) Levitt, M. H. (Tumor Pathology Branch, NCI, Bethesda, MD, 20014). *Lab Invest* 40(2): 268-269; 1979. (4 refs)

79-1874 The Pathogenesis and Frequency of Primary Carcinoma after Stomach Surgery. (Ger) Peitsch, W. (Klinik und Poliklinik für Allgemeinchirurgie, Universität Göttingen, Robert-Koch-Strasse 40, D-3400 Göttingen, W. Germany); Becker, H. D. *Chirurg* 50(1): 33-38; 1979.

Several clinical and experimental studies of the incidence of stomach carcinoma (SCa) after surgical (Billroth II) or conservative (nonsurgical) treatment for stomach ulcers are reviewed. Studies in which a large number (≥ 500) patients and an equal number of controls with the same underlying disease were periodically examined during the period 5-30 yr after surgery and in which histological study established the benign nature of the underlying disease revealed that the SCa incidence associated with Billroth II stomach resection ranges from 7% to 16%. Patients who had a Billroth II resection for duodenal ulcers had an SCa incidence of 7%-9%; patients who had a Billroth II resection for stomach ulcers had an incidence of 13%-16%. An SCa incidence of 10.7% was found in stomach ulcer patients who were treated conservatively, without surgery. A similar incidence was found for patients with chronic atrophic gastritis, who were observed for only 10-15 yr after surgery. There are no studies in which conservatively treated patients with duodenal ulcers were followed for a sufficient time (30 yr). Although rats subjected to Billroth II resection have an SCa incidence of 35%-40%, vs 0% in controls, the results of these animal studies are not directly applicable to humans. In the rat studies, healthy gastric tissue is suddenly placed in an unphysiologic position,

while in ulcer patients the mucosa is abnormal before surgery. Furthermore, the growth behavior of rat SCa differs from that of human SCa. The latter rarely infiltrates the jejunum but it does metastasize, unlike rat SCa. This review shows that Billroth II resection without enteroanastomosis in ulcer patients does not cause a markedly higher incidence of SCa compared with that found in similar ulcer patients treated without surgery. (21 refs)

79-1875 Heredity and Gastrointestinal Tract Cancer. (Eng) Lynch, H. T. (Dept. Preventive Medicine/Public Health, Creighton Univ. Sch. Medicine, Omaha, NE, 68178); Lynch, P. M. In: *Gastrointestinal Tract Cancer*. Lipkin, M.; Good, R. A., eds. (New York, London: Plenum Medical Book Co.): Sloan Kettering Inst. Cancer Series 602 pp.; pp. 241-274; 1978.

The role of genetic factors in the etiology of gastrointestinal (GI) tract cancers is surveyed. Environmental factors appear to be responsible for most malignant neoplasms of the oral cavity, esophagus, liver, and pancreas. However, there is convincing evidence that hereditary factors play a role in tylosis palmaris et plantaris, hereditary pancreatitis, and autosomal dominantly inherited conditions predisposing to esophageal and pancreatic carcinoma. Certain remarkable kindreds such as those exhibiting ataxia-telangiectasia have an identifiable gastric cancer association. Others have manifested gastric carcinoma through multiple generations, with evidence of immunodeficiency being present in high-risk relatives. Additional traits or diseases that have been associated with gastric cancer in the general population include blood group A, pernicious anemia, atrophic gastritis, and achlorhydria, each of which appears to have a familial or genetic component. Autosomal dominantly inherited Peutz-Jeghers syndrome and celiac disease appear to predispose to cancer of the small intestine and possibly other anatomical sites. Colon cancer susceptibility has been associated with familial polyposis coli, Gardner's syndrome, Turcot's syndrome, and generalized GI polyposis. Although a few primary genetic associations have been described in the GI system, the variable interaction of environmental and genetic factors undoubtedly influences cancer frequency. (170 refs)

79-1876 Primary Lymphomas of the Gastrointestinal Tract. I. Plasma Cell Tumors. (Fre) Henry, K. (No affiliation given); Farrer-Brown, G. *Gastroenterol Clin Biol* 2(12): 1058-1059; 1978.

A previously published article concerning a series of 125 patients with lymphomas of the gastrointestinal tract is reviewed briefly. This series was the first to have a significant percentage of plasmacytomas (49%) among gastrointestinal lymphomas. (13 refs)

- 79-1877 The Transformation Zone.** (Eng) Coppleson, M. (King George V. Hosp., Sydney, Australia). In: *Cervical Pathology and Colposcopy. Selected Papers from the Second World Congress of Cervical Pathology and Colposcopy held in Graz, Austria, 15-18 October 1975.* Burghardt, E.; Holzer, E.; Jordan, J. A., eds. (Stuttgart: Georg Thieme Publishers): 146 pp.; 78-80; 1978.

Exposure of ectocervical columnar epithelium to the lower pH of the vagina that occurs at birth, during menarche, or during the first pregnancy results in squamous metaplasia; the end result is a typical or an atypical transformation zone. The former is first seen colposcopically as a fusion of preexisting columnar-epithelial-covered villi with persistence of its dissected surface contours; later, the surface is flattened. White epithelium, punctation, mosaic, atypical vessels, leukoplakia, increased nuclear density, abnormal intraepithelial capillaries, or a keratin covering may be observed in an atypical transformation zone, the site of dysplasia and preclinical carcinoma. (no refs)

- 79-1878 Teratomas and Chimeras.** (Eng) Illmensee, K. (No affiliation given); Stevens, L. C. *Sci Am* 240(4): 120-132; 1979.

Teratomas originate from germ cells and are composed of neoplastic cells plus many kinds of differentiated cells and tissues at various stages of maturation. Teratomas that contain embryonal carcinoma cells continue to grow and are malignant (teratocarcinomas), but those in which the embryonal cells differentiate into various kinds of normal tissue are benign. The malignant stem cells can differentiate normally in the mouse embryo and give rise to chimeras, or genetic mosaics. (no refs)

- 79-1879 Is the Role of the Environment in Carcinogenesis Overestimated?** (Eng) Calabrese, E. J. (Div. Public Health, Univ. Massachusetts, Amherst, MA, 01003). *Med Hypotheses* 5(1): 5-14; 1979.

The role of environmental factors in carcinogenesis is critically reviewed. Despite the fact that environmental factors may initiate and/or promote carcinogenesis, the claim that 85%-90% of all cancers are environmentally related, while probably accurate, is misleading because it neglects the role of the individual's health status as influenced by genetic and nutritional factors. For example, certain racial groups, particularly those of Celtic origin, are significantly more predisposed to the development of UV-induced skin cancer than other whites. Toxicological evidence supports the position that a person's genotype plays a potentially important role in modifying one's susceptibility to arylamine-induced bladder cancer. There also appear to be differences in individual susceptibility to aromatic hydrocarbon-induced bronchogenic carcinoma. Individuals whose lymphocytes metabolize

benzo(a)pyrene via arylhydrocarbon hydroxylase at a high rate following exposure to inducers are suspected of having an increased risk of lung cancer development following long-term exposure to cigarette smoke. Dietary deficiencies of vitamin A and riboflavin have been shown to enhance the development of epithelial cancers in animals exposed to carcinogenic aromatic hydrocarbons. Various epidemiological studies have demonstrated the existence of an inverse association between the incidence of gastric cancer and the consumption of food high in vitamin C. It thus appears that an individual's adaptive capacity may be a critical factor affecting the development of certain environmentally related cancers. (61 refs)

- 79-1880 Mortality for Cancer of the Corpus Uteri (2 Letters to Editor).** (Eng) Miller, A. B. (NCIC Epidemiology Unit, Univ. Toronto, Toronto, Ontario, Canada). *Can Med Assoc J* (11): 1275-1276; 1978.

The importance of distinguishing clearly between cancer of the corpus uteri and cervical cancer so that trends in incidence and mortality can be accurately assessed is discussed in a letter of comment and in a letter of response. Data collection methodologies in three Canadian provinces and some of the resulting data are summarized, and a plea for unambiguous recording of the cause of death is made. (7 refs)

- 79-1881 Current Concepts on the Histogenesis, Pathology, and Immunochemistry of Germ Cell Tumors of the Testis.** (Eng) Nochomovitz, L. E. (No affiliation given.); Rosai, J. *Pathol Annu* 13(1): 327-362; 1978.

The pathology and immunochemistry of germ cell tumors of the testis are reviewed. Classical seminoma accounts for 30%-40% of testicular neoplasms. Morphologically, it is composed of sheets of uniform polyhedral cells segregated into compartments by slender fibrous septa containing a lymphocytic infiltrate. Spermatocytic seminoma is a rare tumor that usually occurs in older men. The tumor cells form sheets without segregation into compartments. Embryonal carcinoma, which constitutes about 20% of all testicular tumors and occurs most frequently in the third decade of life, has a tendency to metastasize widely. Adult teratoma represents 5%-10% of testicular neoplasms. In spite of its benign histologic appearance, it can metastasize and cause death. Mature cartilage and smooth muscle are frequently seen, and the cysts are lined by alimentary, respiratory, or squamous epithelium. Teratocarcinoma, which accounts for 20%-30% of testicular tumors, is distinguished from adult teratoma by the presence of malignant elements in addition to fully differentiated tissue. Choriocarcinoma, which is highly malignant, is usually present as a component of a larger germ cell tumor. It consists of bizarre multinucleated syncytiotrophoblastic cells intermingled with compact sheets of cytotrophoblastic cells. Yolk sac tumor of the testis usually occurs in infants

and children < 3.5 yr of age. Its microscopic pattern reflects elements of the differentiating yolk sac. Elevated levels of α -fetoprotein and β -human chorionic gonadotropin have been detected in patients with nonseminomatous germ cell tumors. Germ cell tumors spread mainly by lymphatics to the common iliac and paraaortic lymph nodes. (155 refs)

- 79-1882 Irradiation Related Thyroid Cancer: History and Current Recommendations.** (Eng) Stockwell, R. M. (Univ. Connecticut Sch. Medicine, Farmington, CT). *Conn Med* 43(2): 63-67; 1979.

The origin and historical development of irradiation as a treatment for benign diseases of the thymus, head, and neck and the relationship of this therapy to thyroid cancer are reviewed. (17 refs)

- 79-1883 Unit of Epidemiology and Biostatistics.** (Eng) Muir, C. S. (International Agency Res. Cancer, Lyon, France). *IARC Annual Report* 19-43; 1978.

A progress report on various areas of research conducted by the Unit of Epidemiology and Biostatistics of the International Agency for Research on Cancer is presented. The Agency continues to play a coordinating role in the field of descriptive epidemiology. The aim of the program of descriptive epidemiology is to map the occurrence of cancer throughout the world and to improve the comparability of incidence data. The existence of differences in cancer risk in different populations facilitates the formulation and testing of etiological hypotheses by the Agency and other bodies. The search for etiological factors in esophageal cancer continues, particularly in the Caspian littoral of Iran and in Normandy. The Unit also is coordinating an extensive series of international studies to explore the role of alcoholic beverages in neoplasia. These studies are currently being extended to Switzerland and Belgium. An international case-control study of the roles of tobacco, alcohol, and occupation in laryngeal cancer has been undertaken. Reasons for the high lung cancer mortality in Cuban women are also being examined by a case-control study, and studies of lung cancer in Cantonese women continue. The effects of diet on colon cancer are being evaluated in Denmark and Finland. The occupational carcinogenesis study program has been expanded. The biostatistical section is evaluating the efficacy of screening programs for the early detection of cervical cancer in relation to mortality and optimum screening intervals. A monograph on modern techniques in the analysis of case-control studies is near completion. (42 refs)

- 79-1884 Epidemiological Identification of Cancer Hazards.** (Eng) Muir, C. S. (Unit Epidemiology and Biostatistics, International Agency Res. Cancer, Lyons,

France). In: *Prevention and Detection of Cancer. Part II. Detection. Vol. 1 High Risk Markers. Detection Methods and Management.* Neiburgs, H. E., ed. (Marcel Dekker, Inc.: New York): 1299 pp.; 3-23; 1978.

Epidemiologic approaches to the identification of cancer hazards are reviewed. As a basis on which to formulate hypotheses, the epidemiologist can examine the behavior of the disease itself with regard to age and sex patterns, geographical distribution between and within countries, variations in histologic type, changes over time and in migrant populations, and clinical observations. These data can then be used to formulate a hypothesis that can be tested by epidemiologic techniques, including case/control and prospective studies. Examples of these techniques are presented. The results of epidemiologic studies have shown that the majority of human cancers are probably due to environmental agents, acting singly or in combination. These agents are of two major types: powerful carcinogens acting on a relatively small number of workers and with generally unknown significance for the general population; and widely distributed agents such as tobacco smoke and excessive exposure to sunlight, over which there is a large measure of personal control. With regard to prevention of carcinogenesis by these agents, much has to be done by the government to protect worker and community. (37 refs)

- 79-1885 The Digestive Form of α -Chain Disease.** (Eng) Seligmann, M. (Lab. Immunochemistry and Immunopathology--INSERM U 108, Res. Inst. Blood Diseases, Hopital Saint-Louis, Paris 10, France); Rambaud, J. C. In: *Gastrointestinal Tract Cancer.* Lipkin, M.; Good, R. A., eds. (New York, London: Plenum Medical Book Co.): Sloan Kettering Inst. Cancer Series 602 pp.; pp. 119-141; 1978.

The epidemiology, clinical features, pathology, immunochemical diagnosis, course, treatment, and pathogenesis of digestive α -chain disease are reviewed, together with the results of structural and cellular studies of the immunoglobulin (Ig) abnormality and the relationship between this disease and "Mediterranean lymphoma." α -Chain disease is a proliferative disorder of B-lymphoid cells involving primarily the IgA secretory system, in which plasma cells produce a presumably homogeneous population of Ig molecules consisting of incomplete α chains devoid of light chains. Most affected patients are between 10 and 30 yr old. The digestive form is rare in developed countries. The disease is usually revealed by severe malabsorption syndrome. The intestinal lesions usually predominate in the duodenum and jejunum, and they are characterized by plasma cell infiltration. The diagnosis is usually suspected or established by immunoelectrophoretic analysis of the serum proteins. There appears to be an early premalignant stage of the digestive form of α -chain disease that progresses to a fatal malignancy. The frequency of this disease among populations exposed to conditions of poor hygiene and the evidence for complete remissions induced in the early stage by po antibiotic therapy implicate environmental

factors in the pathogenesis of the disorder. The evidence suggests that α -chain disease probably represents a model of a lymphoma characterized by a continuous sequence of events ranging from an apparently benign hyperplastic process to overt neoplastic proliferation. Analysis of the sequence of events occurring between the premalignant and malignant stages may offer insight into the development of lymphomas in humans. (62 refs)

- 79-1886 Epidemiology of Esophageal Cancer.** (Eng) Haas, J. F. (Cornell Univ. Medical Coll., New York, NY, 10021); Schottenfeld, D. In: *Gastrointestinal Tract Cancer*. Lipkin, M.; Good, R. A., eds. (New York, London: Plenum Medical Book Co.): Sloan Kettering Inst. Cancer Series 602 pp.; pp. 145-172; 1978.

The geographical pathology, demographic characteristics, and etiology of esophageal cancer (EC) are reviewed. Dramatically different patterns of occurrence are observed for EC in different parts of the world, among different ethnic groups, and in men and women. There is no unifying hypothesis to explain the varied epidemiological picture presented by EC in different regions of the world. This picture suggests that there is more than one environmental determinant. Alcohol apparently plays a role in the development of EC, particularly in North America and Europe, although there is no evidence that it acts directly as a carcinogen. Tobacco smoking, closely tied with alcohol consumption, seems to make an independent contribution to EC. Smoking induces dose-related histological changes in the esophageal squamous epithelium that are strongly reminiscent of those preceding bronchogenic carcinoma. In areas such as the Caspian littoral, where EC is not tobacco- or alcohol-related, dietary factors are of special concern. Geophysical environment may be reflected in the effect of local soil characteristics on diet. Molds productive of carcinogens could be geographically limited food contaminants. Mucosa conditioned by chronic specific nutritional deficiency may be especially vulnerable to the action of carcinogens. (106 refs)

- 79-1887 Bronchopulmonary Tumors: Epidemiology.** (Ita) Renga, G. (Istituto di Igiene, Università degli Studi di Ancona, Ancona, Italy). *Minerva Med* 70(3): 173-194; 1979.

Epidemiological and etiological data on lung cancer are reviewed. In Europe, lung cancer mortality is $> 100/100,000$ in England; $61-99/100,000$ in Germany, Switzerland, Austria, Denmark, Netherlands, Belgium, and Finland; $31-60/100,000$ in Poland, Bulgaria, Greece, Hungary, Italy, France, Ireland, and Sweden; and $16-30/100,000$ in Yugoslavia, Spain, Portugal, Romania, Norway, and Iceland. In Italy, a positive correlation was found between the size of a city in terms of population and lung cancer mortality. Air pollution, occupational exposure to harmful substances, and

smoking are considered the principal environmental factors of lung cancer. Industrial pollutants suspected of inducing lung cancer in humans include uranium, radon, hematite, polycyclic aromatic hydrocarbons, asbestos, arsenic, chromium, nickel, mustard gas, acrylonitrile, chloromethyl ether, and, possibly, beryllium and vinyl chloride. Carcinogens detected in tobacco smoke include dimethylnitrosamine, diethylnitrosamine, methylethylnitrosamine, N-nitrosopyrrolidine, nitrosopiperidine, benzo(a)pyrene, methylbenzo(a)pyrene, dibenzoacridine, dibenzocarbazole, β -naphthylamine, benzo(a)fluoranthene, methylfluoranthene, benzantracene, chrysene, nitrosoanabasine, benzophenanthrene, nitrosonornicotine, polonium-210, and arsenic. (55 refs)

- 79-1888 The Natural History of Lung Cancer: A Review Based on Rates of Tumour Growth.** (Eng) Geddes, D. M. (Brompton Hosp., London, England). *Br J Dis Chest* 73(1): 1-17; 1979.

The natural history of lung cancer is formulated based on a review of tumor growth rates. The exponential model of tumor growth, which predicts that tumor doubling goes on at a constant rate, fits the observed facts reasonably well. To calculate the natural history of a solid tumor that grows exponentially, the doubling time, size at diagnosis, and total tumor mass at death need to be known. Pooling the doubling times of lung cancer reported in the literature, the time from malignant change to diagnosis is calculated to be approx 10 yr and, following diagnosis, the av time to death is approx 18 mo. Predicted survival curves were calculated from time of diagnosis for different-sized tumors based on the distribution of their doubling times. The curves for different histological types of tumors show marked differences, with adenocarcinoma patients surviving longer than those with squamous tumors. The natural history calculated according to this model correlates well with several clinical observations. The long delay between the start of smoking and the appearance of lung cancer suggests that prolonged stimulation is necessary or that there is some efficient anti-tumor defense system that becomes less effective with age. The 5-yr survival in lung cancer varies from 5% to 9%, a range similar to that predicted from growth rates. Earlier diagnosis and treatment are not likely to influence lung cancer survival rates to any great extent. (32 refs)

- 79-1889 Epidemiology of Gastric Cancer.** (Eng) Haas, J. F. (Cornell Univ. Medical Coll., New York, NY, 10021); Schottenfeld, D. In: *Gastrointestinal Tract Cancer*. Lipkin, M.; Good, R. A., eds. (New York, London: Plenum Medical Book Co.): Sloan Kettering Inst. Cancer Series 602 pp.; pp. 173-206; 1978.

The epidemiology of gastric cancer (GC) is reviewed, with regard to pathology, relation to gastric polyps, time trends, personal risk factors, racial and ethnic differences in distribu-

tion in the US, nativity and migrant studies, social class and occupational factors, familial and hereditary influences, pathogenesis and etiology and models of its etiology. A precipitous decline in death rates from GC has occurred at a time of slowly rising mortality from all cancers. GC frequency varies dramatically throughout the world. Two highly industrialized societies, Japan and the US, are near the top and bottom, respectively, of the rank order of GC mortality by country. Similarly, Chile and Mexico, although only modestly industrialized, show a fivefold difference in GC mortality. Even within countries with uniform reporting and classification systems, GC mortality may show marked differences from area to area. GC is more frequent in men than in women in all settings, and its incidence and mortality rates rise steeply with age. The importance of racial differences in susceptibility to GC is unclear. Migrant studies indicate that persons moving from high- to low-risk areas retain a considerable excess risk compared with natives of low-risk areas. GC risk is greatest among the poor. For metal workers, miners, rubber workers, and workers exposed to wood dusts and asbestos, there is evidence that specific occupational hazards may exist for GC. Epidemiological investigations of the pathogenesis and etiology of GC have suggested links between this disease and blood group, pernicious anemia, intestinal metaplasia, and diet (including exposure to nitrosamines and polycyclic hydrocarbons). Recent efforts to consolidate information on GC into an etiological model have concentrated on mechanisms by which the mucous barrier of the stomach might be damaged, exposing the epithelium to carcinogens. (117 refs)

- 79-1890** **Ulcerative Colitis and Colon Cancer.** (Swe)
Brostrom, O. (Gastroenterologiska sektionen, Sodersjukhuset, Stockholm, Sweden); Nystrom, B.; Reichard, H.; Ost, A. *Lakartidningen* 76(3): 99-100; 1979.

Studies of the relationship between ulcerative colitis and colon cancer are reviewed. The incidence of colon cancer is relatively low among ulcerative colitis patients, with cancer developing most often before age 50 yr. Seven cases of colon cancer were found in a series of 220 patients with ulcerative colitis diagnosed during 1945-1964 and followed until 1975. Colon cancer can be prevented by proctocolectomy, but this procedure should be restricted to patients at risk. Risk factors for colon cancer in ulcerative colitis are total colitis; chronic, continuous colitis as opposed to an intermittent course; duration of colitis > 10 yr; and, possibly, onset of colitis at a young age. In a prospective epidemiological study, the incidence of colon cancer was 0/229 patients with total colitis lasting < 10 yr, 2/392 combined observation years (COR) among patients with colitis > 11-20 yr, and 3/181 COR among patients with colitis > 20 yr. (9 refs)

- 79-1891** **Epidemiology of Colorectal Cancer.** (Eng)
Schottenfeld, D. (Dept. Epidemiology and Pre-

ventive Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Haas, J. F. In: *Gastrointestinal Tract Cancer*. Lipkin, M.; Good, R. A., eds. (New York, London: Plenum Medical Book Co.); Sloan Kettering Inst. Cancer Series 602 pp.; pp. 207-240; 1978.

The epidemiology of colorectal cancer is reviewed. Colorectal cancer is the most common newly diagnosed malignancy in the US. Adenocarcinomas are overwhelmingly the most prevalent histological type; histological subgroups of mucin-producing tumors may be of both etiological and prognostic importance. The ratio of colon cancer (CC) to rectal cancer (RC) incidence rates is correlated with overall incidence of large intestine cancer. The proportion of CC's is highest in high-incidence areas. Where the rates for both tumors are low, the proportion of RC's is relatively high. Even within countries, marked variation may occur in the frequency of cancers of the large intestine. Countries subject to a high incidence of CC demonstrate a relatively higher frequency of sigmoid cancers, whereas in low-risk countries cancers of the cecum and ascending colon predominate. The age-specific incidence rates of both CC and RC rise steadily from ages 10-14 to 80-84. RC is more prevalent among men in most countries, whereas CC affects both sexes at similar rates. Differences between US whites and nonwhites with respect to CC mortality were marked before 1950, but subsequent years have seen a steady convergence as a result of increasing rates among nonwhites. Migration studies have suggested that environmental influences later in life can affect the risk of CC. Studies in Japan, Colombia, and the US demonstrated a higher CC incidence among the upper social classes. Diseases that may be associated with large intestine cancer include ulcerative colitis and Crohn's disease. There is also an apparent association with diseases causing the development of adenomatous polyps in the colon and rectum. Possible dietary factors that contribute to colorectal cancer include reduced fiber intake and increased meat consumption. Studies concerning the effects of these and other dietary factors on intestinal microflora and metabolism are reported. (89 refs)

- 79-1892** **The Epidemiologic Approach to the Evaluation of Organics in Drinking Water.** (Eng) Cantor, K. P. (U.S. Environmental Protection Agency, Cincinnati, OH, 45268); McCabe, L. J. *Water Chlorination* 2: 379-393; 1978.

Epidemiologic methods of evaluating the cancer hazard posed by contaminants in drinking water are reviewed, as are some studies that have utilized these methods. The hypotheses upon which a study may be based may originate from laboratory experiments combined with information on environmental exposures to humans, the observations of astute clinicians, and geographical and temporal comparisons of the rates of exposure and disease in human populations. Ecologic studies, which correlate the geographical distribution of disease with environmental factors, are relatively inexpensive and can be completed quickly. However, they have only a

limited ability to take account of possible confounding factors and should be used only to provide qualitative guides to risks. Case-control and cohort studies are valuable in testing hypotheses and in developing quantitative estimates of health risks related to particular exposures or personal characteristics. They are, however, more costly and time-consuming than ecologic studies. Several ecologic studies have investigated the potential cancer risk associated with chlorination and/or organics in drinking water supplies. Bladder and colon/rectal cancer mortality was correlated with the water quality parameter in several of these studies. Analytic studies based on information from cancer patients and appropriately matched controls are now imperative to evaluate a possible causal relationship. (23 refs)

- 79-1893 Epidemiology of Carcinoma of the Cervix.** (Eng) Miller, A. B. (Epidemiology Unit, Natl. Cancer Inst. Canada, Dept. Preventive Medicine and Biostatistics, Univ. Toronto, 121 St. Joseph St., Toronto, Ontario, M5S 2R9, Canada). In: *Cervical Pathology and Colposcopy. Selected Papers from the Second World Congress of Cervical Pathology and Colposcopy held in Graz, Austria, 15-18 October 1975*. Burghardt, E.; Holzer, E.; Jordan, J. A., eds. (Stuttgart: Georg Thieme Publishers): 146 pp.; 103-111; 1978.

Epidemiological studies of carcinoma of the cervix are reviewed. In practice, carcinoma of the cervix has been shown to have a higher incidence in urban populations than in rural populations, in the lower social classes than in the upper social classes, in Negroes in the US than in whites, in married women than in single women, in widowed or divorced women than in married women, in multiparas than in nulliparas, in women married early than in those married later, in women with a first pregnancy at a young age than in those with first pregnancy at an older age, in those who were sexually initiated in adolescence than in those who were initiated after adolescence, in women with a history of syphilis than in those without such a history, and in those with several sexual partners than in those with only one partner. The correlation for some of these variables is highly significant. The effects of age at first marriage and age at first pregnancy disappear when the data are controlled for age at first intercourse. There is also a body of evidence that suggests that herpes virus type 2, which is primarily transmitted by sexual contact, may be etiologically related to carcinoma of the cervix. Some

variables that have been suspected as being associated with a higher incidence of carcinoma of the cervix are clearly not related when a number of studies are considered. Such variables include coital frequency, mean age at menarche, contraceptive practices, and partner not circumcised. (11 refs)

- 79-1894 Causes of Cancer (Letter to Editor).** (Eng) Peto, R. (Radcliffe Infirmary, Oxford, England). *Nature* 277(5696): 428; 1979.

The claim that many, and perhaps most, cancers are caused by certain sexual habits, smoking, and diet rather than by environmental pollutants is substantiated. Smoking is responsible for about 30% of all British cancer deaths. Uterine cervical cancer is much more common in prostitutes than in nuns, and it is commoner among women who have had many sexual partners or who begin intercourse at an early age. Carcinogenesis in rats pretreated with carcinogens is affected by increases or decreases in certain dietary fats, and fat consumption in humans has been related to the development of colon and breast cancer. (4 refs)

- 79-1895 Industrial Cancer--Whose Responsibility?** (Eng) Alderson, M. (Inst. Cancer Res., Sutton, Surrey, England). *Ann Occup Hyg* 21(3): 285-291; 1978.

The problems of industrial cancer and its control are surveyed. Cancer control depends on the collaboration of central government, industry, unions, medical personnel, research teams, and the general public. Research studies should be based on the best hypotheses derived from clinical experience, laboratory investigations, and epidemiology. After research has demonstrated and quantified a risk, plans must be laid for preventing further disease. In this, the advantages of control must be balanced against economic and other hardships caused by stringent regulation of the use of a particular substance. Primary prevention aims at removing the carcinogenic agent or reducing exposure, whereas secondary prevention aims at identifying disease at a stage at which treatment can be applied and will be successful. The latter must be considered whenever a long-standing hazard has been identified. It should involve both screening for disease and education of exposed workers. (15 refs)

CHEMICAL CARCINOGENESIS

- 79-1896 **Chemical Carcinogenesis: Dose-Response Extrapolation (Letter to Editor).** (Eng) Clayson, D. B. (Office Deputy Director, Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NE, 68105). *Science* 203(4385): 1068-1069; 1979.

In dose-response extrapolation, the further one extrapolates from the data base, the greater the level of uncertainty in the predictions. In cancer induction, the uncertainties in extrapolation are compounded by the complexity of the process and the vast number of factors, such as promoting agents, that may drastically affect tumor yield. (no refs)

- 79-1897 **Determination of Fecal Mutagens (Meeting Abstract).** (Eng) Kuhnlein, H. V. (Univ. British Columbia, Vancouver, BC V6T 1W5, Canada); Stich, H. F. *Fed Proc* 38(3, part 1): 713; 1979. (2 refs)

- 79-1898 **Asbestos Dust Standard (Letter to Editor).** (Eng) Woolf, A. D. (24 Deepdene Road, Denmark Hill, London SE5 8EG, England). *Ann Occup Hyg* 21(3): 327; 1978.

The official establishment of asbestos dust standards in 1969, following recommendations of the British Occupational Hygiene Society, was based on information that was inadequate as the justification for setting an officially approved 'safe' asbestos level. This conclusion has since been reached by the Health and Safety Executive Advisory Committee on Asbestos as well. (1 ref)

- 79-1899 **The Routine Monitoring of Airborne Asbestos in an Occupational Environment.** (Eng) Richards, A. L. (TBA Industrial Products Ltd., T & N Ltd., P.O. Box 22, Trafford Park, Manchester, England). *Ann Occup Hyg* 21(3): 315-322; 1978.

Techniques and strategy used in the routine monitoring of airborne asbestos in a major asbestos textile factory employing approx 1,500 persons are described. It was possible to assess the biological effects of asbestos by personal membrane-filter sampling, to control the general factory environment with the use of particle counters, and to study working practices with both measuring techniques. (3 refs)

- 79-1900 **Nucleic Acid Metabolism in the Rat Following Short-Term and Prolonged Ingestion of Chrysotile Asbestos or Cigarette-Smoke Condensate.** (Eng) Jacobs, R. (Dept. Biochemistry, Univ. Coll., P.O. Box 78, Cardiff CL1 1XL, Wales); Weinzwieg, M.; Dodgson, K. S.; Richards, R. J. *Br J Exp Pathol* 59(6): 594-600; 1978.

The effects of chrysotile asbestos or cigarette smoke condensate ingestion on DNA and RNA metabolism were studied in various tissues of 3-mo-old male MRC hooded rats. The rats received asbestos (50 mg/day) for 1 wk or for 5-15 mo. Rats treated for either the short- or long-term periods showed statistically significant increases in [³H]thymidine incorporation into DNA in the small intestinal mucosa, colon, rectum, and stomach, and spleen and a significant decrease in the incorporation of this radiolabel into liver DNA. Short-term asbestos ingestion did not affect [³H]uridine incorporation into RNA of any tissue, but long-term treatment significantly increased incorporation in lung RNA and decreased incorporation in liver RNA. Short-term ingestion of a diet containing cigarette smoke condensate produced significant increases in [³H]uridine incorporation into RNA in the small intestinal mucosa, submucosa, spleen, and heart. Long-term ingestion of this diet produced similar changes in the submucosa, spleen, and lung. It is concluded that the apparent specificity and the mechanism(s) whereby ingested asbestos induces changes in nucleic acid metabolism require further experimentation. (27 refs)

- 79-1901 **Effects of Chronic Asbestos Ingestion on ¹²⁵I-UdR Incorporation in Various Tissues of Mice (Meeting Abstract).** (Eng) Joel, D. D. (Medical Dept., Brookhaven Natl. Lab., Upton, NY, 11973); LeFevre, M. E. *Fed Proc* 38(3, part 2): 1352; 1979. (1 ref)

- 79-1902 **Alkali Metal Salts and Tumor Growth: A Paradoxical Response (Meeting Abstract).** (Eng) Messiha, F. S. (Texas Tech Univ. Sch. Medicine, Lubbock, TX, 79430); El-Domeiri, A.; Hsia, W. C. *Fed Proc* 38(3, part 1): 701; 1979. (no refs)

- 79-1903 **An Autopsy Case of Pulmonary Asbestosis, Peritoneal Mesothelioma, and Incidental Stomach Cancer.** (Jpn) Hiasa, Y. (Dept. Pathology, Nara Medical

Univ., Nara, Japan); Ohjima, M.; Iwata, M.; Miyadai, A.; Yagai, R.; Murata, Y.; Yamada, K.; Ozono, S.; Shimamoto, K.; Tsujimoto, H.; Okajima, E. *Gan No Rinsho* 25(2): 124-132; 1979.

The case report of a 62-yr-old man who, upon autopsy examination, was found to have pulmonary asbestosis, peritoneal mesothelioma, and stomach cancer is presented, and literature concerning mesothelioma patients is reviewed. The man had worked in an asbestos plant for about 30 yr, had been a moderately heavy smoker (1 pack/day), and had a history of tracheal inflammation (cough and expectoration) since the age of 45. The patient was first treated for prostatic concretions. Complaints of stomach pain 3 mo later led to a diagnosis 2 mo later of adenocarcinoma of the jejunum. The patient died shortly thereafter. Autopsy revealed a sheet of gray-white tumor covering the serosal surface of the large bowel and stomach but not involving the mucosa. The inferior side of the diaphragm was covered with tumors. Histological studies showed mesothelioma and an incidental stomach adenocarcinoma. Microscopically, numerous asbestos bodies were found within fibrous areas in the alveolar walls and in the smaller bronchial branches. The literature showed that asbestosis was associated with 22/26 pleural mesothelioma cases and 5/7 peritoneal mesothelioma cases. (25 refs)

79-1904 Correlation Between Iron-induced Lipoperoxidation and "Unscheduled" DNA Synthesis in Isolated Nuclei and Cultured Hepatocytes (Meeting Abstract). (Eng) Shires, T. K. (Dept. Pharmacology, Univ. Iowa, Iowa City, IA, 52242); Lovig, C. *Fed Proc* 38(3, part 2): 1404; 1979. (no refs)

79-1905 Lithium Reinduction of Acute Myeloblastic Leukemia (Letter to Editor). (Eng) Orr, L. E. (Southern California Cancer Center, California Hosp. Medical Center, Los Angeles, CA, 90015); McKernan, J. F. *Lancet* 1(8113): 449-450; 1979.

The case of a patient in whom acute myeloblastic leukemia apparently was reinduced by lithium treatment is presented. Li treatment (300 mg, bid) was started for persistently low neutrophil counts and recurrent bacterial infections during the nadir of maintenance chemotherapy. Reinduction occurred 7 wk later. Li could, theoretically, have caused recruitment of granulocyte precursors from a resting to a growing state. (5 refs)

79-1906 Histological Changes in Nasal Mucosa of Workers in an Electrolytic Nickel Refinery (Meeting Abstract). (Eng) Solberg, L. A. (Ullevål Hosp., Univ. Oslo, Oslo, Norway); Torjussen, W. *Ann Clin Lab Sci* 8(6): 503; 1978. (no refs)

79-1907 Rapid Measurement of Carcinogen-induced DNA Damage Using Mitogen-stimulated Lymphocytes (Meeting Abstract). (Eng) Warren, J. R. (Dept. Pathology, Northwestern Univ. Medical Sch., Chicago, IL, 60611). *Fed Proc* 38(3, part 2): 1403; 1979. (no refs)

79-1908 Growth Factor Requirements of Chinese Hamster Cell Hybrids, Clonal Progeny, and Tumorigenic Derivatives (Meeting Abstract). (Eng) Sager, R. (Sidney Farber Cancer Inst., Boston, MA, 02115); Cherington, P. V.; Smith, B. L.; Pardee, A. B. *Fed Proc* 38(3, part 1): 635; 1979. (1 ref)

79-1909 Changes in beta-Glucuronidase Activity in WBC of Rats Exposed to Benzene, and Protective Treatment with Selenium. (Pol) Moszczynski, P. (Katedra Medycyny Pracy i Chorob Zawodowych AM, skr. poczt. 13, 30-969 Krakow, Poland); Starek, A. *Med Pr* 29(5): 379-385; 1978.

The effect of benzene inhalation (1,200 mg/m³, 6 hr/day, 6 days/wk, for 2 wk) on lysosomal β -glucuronidase (BG) activity and the protective effect of selenium pretreatment (1 or 5 μ g/kg po on 10 consecutive days) were studied in 32 male Wistar rats aged about 4 mo. Exposure to benzene alone significantly decreased BG activity in the neutrophils from 35.8 to 18.2 units ($p < 0.01$) and the lymphocyte count from 9,110/ μ l to 5,300/ μ l ($p < 0.001$), and it significantly increased the percentage of BG-positive lymphocytes from 85.9% to 93.5% ($p < 0.001$). Pretreatment with 1 μ g/kg Se failed to prevent the lymphocytopenia, but it prevented the decrease in neutrophil BG activity and the damage to the lysosomes. Pretreatment with 5 μ g/kg prevented the lymphocytopenia, increased the number of neutrophils, and prevented the decrease in neutrophil BG activity, but it increased the BG-positive lymphocyte fraction, especially lymphocytes in which the enzyme was localized in the cytoplasm. The results indicate that the lysosomal membranes of the lymphocytes were protected from the toxic effects of benzene by the smaller dose of Se, whereas both doses protected the neutrophil BG activity. (30 refs)

79-1910 Note on Microbiological and Aflatoxin Analyses of Cereal Grains from the Tarai Plain of Southern Nepal. (Eng) Karki, T. B. (Food Res. Div., Dept. Food and Agriculture Marketing Services, Bafarmahal, Katmandu, Nepal); Bothast, R. J.; Stubblefield, R. D. *Cereal Chem* 56(1): 41-42; 1979.

A preliminary study in which microbiological and aflatoxin analyses of cereal grains from the Tarai Plain of Southern Nepal were carried out indicated that the microbiologic counts were satisfactory but that all three corn samples con-

tained aflatoxin at levels ranging between 8 and 37.5 ppb. (5 refs)

- 79-1911 The Effect of Selenium on Transplantable Tumor Cells (Meeting Abstract).** (Eng) Poirier, K. A. (Univ. Illinois, Urbana, IL, 61801); Milner, J. A. *Fed Proc* 38(3, part 1): 864; 1979. (no refs)

- 79-1912 Effect of Dietary Fiber on Azoxymethane-induced Intestinal Carcinogenesis in Rats.** (Eng) Nigro, N. D. (Dept. Surgery, Wayne State Univ. Sch. Medicine, 540 E. Canfield Ave., Detroit, MI, 48201); Bull, A. W.; Klopfer, B. A.; Pak, M. S.; Campbell, R. L. *J Natl Cancer Inst* 62(4): 1097-1102; 1979.

The effect of alfalfa, bran, and cellulose on intestinal tumor formation and fecal biliary steroid levels was studied in male Sprague-Dawley rats treated with azoxymethane (AOM). Animals received weekly sc injections of 8 mg AOM/kg and were fed diets containing 10% fiber (wt/wt) and 35% beef fat or 20% or 30% fiber and about 6% beef fat. Control animals in each instance were fed fiber-free diets. All animals were killed after 23 wk. The addition of 10% fiber to the high-fat diet did not significantly reduce the intestinal tumor frequency (av number of tumors/rat = 7.6-9.5, vs 8.44 in fiber-free controls). However, addition of 20% or 30% fiber to the 6% fat diet significantly reduced the intestinal tumor frequency (av number of tumors/rat = 1.95-3.79, vs 4.04 in fiber-free controls). The concentration of fecal biliary steroids (mg/g dry feces) was significantly lowered in the groups with reduced tumor frequencies, whereas the total excretion of fecal biliary steroids (mg/day) did not show a similar correlation. It is suggested that intestinal tumor frequency can be reduced by increased diet fiber only when fat intake is not at a high level. The effect of fiber may be due to dilution of promoters and/or carcinogens in the intestinal tract. (16 refs)

- 79-1913 Increased Activation of Procarcinogens after Ethanol (Meeting Abstract).** (Eng) Seitz, H. K. (Veterans Admin. Hosp., Bronx, NY); Garro, A. J.; Lieber, C. S. *Fed Proc* 38(3, part 2): 1404; 1979. (no refs)

- 79-1914 Leukemia in Workers Exposed to Ethylene Oxide.** (Eng) Hogstedt, C. (Dept. Occupational Medicine, Regional Hosp., Orebro, Sweden); Malmqvist, N.; Wadman, B. *JAMA* 241(11): 1132-1133; 1979.

Between 1972 and 1977, leukemia occurred in three persons employed in a Swedish factory in which 50% ethylene oxide and 50% methyl formate were used. A 51-yr-old woman developed chronic myeloid leukemia after 4 yr exposure, a

37-yr-old woman developed acute myelogenous leukemia after 9 yr exposure, and a 56-yr-old man developed primary macroglobulinemia after an estimated exposure of 3 hr/wk for 6 yr. The 8-hr, time-weighted av concentration of ethylene oxide + methyl formate in the breathing zone of the women was calculated as 20 ± 10 ppm. Without consideration of latency time or minimum exposure, the incidence of leukemia in the factory during 1972-1977 would have been expected to be 0.2 case. The women had no known exposure to benzene, radiation, or other leukemia-inducing agents; the man had some occasional contact with benzene in laboratory work. Except for increased bleeding as the initial symptom in all three cases, there were no indications that an aplastic or hypoplastic marrow preceded the appearance of malignancy. Epidemiologic studies of larger populations exposed to ethylene oxide plus reduction of exposure through improved industrial hygiene are recommended. (14 refs)

- 79-1915 Effect of Trichloropropene Oxide and Benzo(a)fluorene on Polycyclic Hydrocarbon Carcinogenesis in C3H/He and DBA/2 Mice.** (Eng) Watanabe, M. (Res. Inst. Tuberculosis and Cancer, Tohoku Univ., Seiryomachi 4-1, Sendai 980, Japan); Watanabe, K.; Sato, H. *Gann* 70(1): 83-87; 1979.

The effects of 1,1,1-trichloropropene 2,3-oxide [TO: 1.2 micromoles (μ mol), sc] and 7,8-benzofluorene (BF: 0.6 μ mol, sc) on the induction of sc fibrosarcoma by 3-methylcholanthrene (3-MC: 0.6 μ mol, sc) and benzo(a)pyrene (BP: 0.6 μ mol, sc) were studied in C3H/He and DBA/2 mice. The chemicals were dissolved in corn oil or triolein and administered in a single dose. TO and, to a lesser extent, BF increased the tumor incidence in DBA/2 mice treated with BP; there was no increase in tumor incidence in DBA/2 mice treated with 3-MC. In the C3H/He mice, TO reduced tumor incidence and prolonged survival time following BP treatment, but it had no effect on tumor incidence following 3-MC treatment. BF had no effect on tumor incidence or survival time. Compared with DBA/2 mice, C3H/He mice showed a higher epidermal aryl hydrocarbon hydroxylase (AHH) activity and a higher incidence of fibrosarcomas with a reduced latency period after BP or 3-MC treatment. The carcinogenicities of BP and 3-MC were similar. Thus, the difference in sc tumor incidence in the two mouse strains may be correlated with epidermal AHH activity. (17 refs)

- 79-1916 Thiodiglycolic Acid: A Major Metabolite of Bis(2-chloroethyl)ether.** (Eng) Lingg, R. D. (Health Effects Res. Lab., U.S. Environmental Protection Agency, Cincinnati, OH, 45268); Kaylor, W. H.; Pyle, S. M.; Tardiff, R. G. *Toxicol Appl Pharmacol* 47(1): 23-34; 1979.

The major in vivo metabolites of bis(2-chloroethyl)ether (BCEE) were identified by gas chromatography/mass spectrometry following administration of a single 40 mg/kg-dose

by po gavage to male Sprague-Dawley rats. Approx 1.6% unaltered BCEE was recovered from the expired air during the first 8 hr after administration; none was recovered between 8 and 48 hr. The methyl ester/trimethylsilyl ether derivatives of the isolated urinary acid fraction yielded two metabolites: thiodiglycolic acid (TDGA) and 2-chloroethyl- β -D-glucosiduronic acid (CEGA). The av recovery of the former during the 48 hr after administration of BCEE was 33.0 mg/kg. The mass spectrum of CEGA prepared in vitro with rabbit liver microsomes was similar to that of the CEGA recovered from the urine of rats treated with BCEE, verifying CEGA as a metabolite of BCEE. (26 refs)

79-1917 Short-Term Toxicity and Reproduction Studies in Rats with Hexachloro-(1,3)-butadiene. (Eng) Harleman, J. H. (Dept. Pathology and Hygiene, Coll. Veterinary Medicine, Univ. Illinois at Urbana-Champaign, Urbana, IL, 61801); Seinen, W. *Toxicol Appl Pharmacol* 47(1): 1-14; 1979.

Wistar-derived rats were given 0.4-15.6 mg/kg/day hexachloro-(1,3)-butadiene (HCBd) by gavage for 13 wk, or 150 or 450 ppm in the diet for 2 wk. The main toxic action of HCBd was in the kidneys. Decreased urine-concentrating ability was found in females at low doses, and extensive tubular degeneration, degeneration and necrosis of individual epithelial cells, plus increased cellularity of the epithelial lining were noted in both sexes at high doses. There were no significant effects on fertility or progeny. (24 refs)

79-1918 Subcutaneous Pristane Injection Enhances the Growth of Plasma Cell Tumor MOPC-315 (Meeting Abstract). (Eng) Platika, M. (Res. Inst. Hosp. Joint Diseases, Mt. Sinai Sch. Medicine, New York, NY, 10035); Bojko, C.; Hollander, V. *Fed Proc* 38(3, part 1): 701; 1979. (no refs)

79-1919 Glycolipids as Indicators of Tumorigenesis. (Eng) Morre, D. J. (Dept. Medicinal Chemistry, Purdue Univ., West Lafayette, IN, 47907); Kloppel, T. M.; Merritt, W. D.; Keenan, T. W. *J Supramol Struct* 9(2): 157-177; 1978.

The nature of the ganglioside (GS) changes that accompany experimental liver tumorigenesis was studied in Wistar rats with hyperplastic liver nodules and hepatocellular carcinomas induced by N-2-fluorenylacetylacetamide (0.025% or 0.05% of the diet for up to 12 mo). Sialic acid and GS sialic acid values increased nearly twofold in the hyperplastic nodules and reached max levels in poorly differentiated, well-circumscribed hepatomas. The levels were also elevated in carcinogen-treated animals before the appearance of nodules or hepatoma and in the apparently normal livers of

rats with transplanted sc hepatomas. The alterations in glycolipid composition appeared to be directly related to alterations in biosynthetic activities. The pattern during tumorigenesis was the inverse of that during normal development. Also, GS patterns showed a progressive simplification from hyperplastic nodules to well-differentiated hepatomas and through two grades of poorly differentiated hepatomas. An increase in the activity of the branchpoint enzyme of GS biosynthesis preceded both a decrease in the branchpoint enzyme of the disialo-GS pathway and a marked increase in the galactosyltransferase of the monosialo-GS pathway. The results indicate that GS deletions are the end result of a cascade of events in malignant transformation, with the onset of GS deletions possibly correlating with the onset of malignancy. Glycolipid levels were elevated early in certain tissues surrounding the tumors, especially the blood. These findings suggest a role for GS's in cancer detection and as regulatory signals for cell growth and multiplication. (77 refs)

79-1920 Histopathologic Differences Between Nitrofen-induced and Naturally Occurring Hepatocellular Carcinomas in the B6C3F1 Mouse (Meeting Abstract). (Eng) Hoover, K. L. (Tumor Pathology Branch, NCI, Bethesda, MD, 20014); Stinson, S. F.; Ward, J. M. *Lab Invest* 40(2): 261; 1979. (no refs)

79-1921 Detection of Mutagens in the Urine of Rats Following Topical Application of Hair Dyes. (Eng) Ammenheuser, M. M. (Dept. Biology, Lamar Univ., Beaumont, TX, 77710); Warren, M. E. *Mutat Res* 66(3): 241-245; 1979.

Rats were treated with two commercial oxidative-type hair-coloring products (dyes A and B), both of which contain the direct dyes 4-nitro-o-phenylenediamine (4NOPD) and 2-nitro-p-phenylenediamine, and their urine was analyzed for the presence of mutagens with the use of *Salmonella typhimurium* strain TA1538. The study was designed to simulate actual hair-dye use conditions. From 10 to 30 ml of dye A or B + an equal volume of hydrogen peroxide were applied to shortened hair on the back of the rat, allowed to remain for 20 min, and then removed by shampooing and thorough rinsing. Urine specimens were collected every 24 hr for 4 days. The same procedure was used for a soln of 120 mg 4NOPD in acetone or isopropanol (IP). Rats were also inoculated ip with 5 mg 4NOPD. Mutagens were detected in rat urine after topical application and ip injection of 4NOPD. There was a fourfold increase in mutagenicity when 4NOPD was applied in acetone rather than IP, but the latter results should be more comparable to actual use conditions since IP is one of the base ingredients of hair-coloring products. The injection study indicated that only 1%-5% of the injected 4NOPD appears in the urine in a form that is directly mutagenic. Mutagens were also detected in the rat urine following application of dyes A and B. Max levels of mutagenicity oc-

curred with urine collected during the first 24 hr. Although the level of mutagenicity was low in all of the assays, a dose-response was observed when increasing volumes of mutagenic urine were tested. Urine samples collected 2-4 days after application did not show statistically significant levels of mutagenicity. The 4NOPD in the two dyes could account for at least some of the mutagenicity of the urine. A number of the other approx 24 ingredients or their reaction products could also contribute urinary mutagens, but they may not be detectable in this particular test system. They may require further metabolic activation or they may not be present in sufficient concentration. (20 refs)

- 79-1922 Neoplasms Induced in the Rat Urinary Bladder by α -Anisidine Hydrochloride (Meeting Abstract).** (Eng) Stinson, S. F. (Tumor Pathology Branch, NCI, NIH, Bethesda, MD, 20014). *Lab Invest* 40(2): 286-287; 1979. (no refs)

- 79-1923 Fluorescence Detection and Determination of Patulin by Thin-Layer Chromatography of Its Aniline Imine.** (Eng) Young, J. C. (Chemistry and Biology Res. Inst., Agriculture Canada, Ottawa, Ontario K1A 0C6, Canada). *J Environ Sci Health B* 14(1): 15-26; 1979.

A sensitive and simple procedure for patulin analysis involves extraction of patulin from the sample, silica gel column chromatographic clean-up, preparation of the aniline imine, thin-layer chromatographic separation on silica gel, hydrogen chloride hydrolysis of the imine, and fluorophore formation from the liberated aniline with fluorecamine. Limit of detection was 5 nanograms. Patulin recoveries from apple juice samples spiked at 50-500 ppb were quantitative. (24 refs)

- 79-1924 Mutagenicity of Plant Flavonols in the Salmonella/Mammalian Microsome Test. Activation of Flavonol Glycosides by Mixed Glycosidases from Rat Cecal Bacteria and Other Sources.** (Eng) Brown, J. P. (Dynapol, 1454 Page Mill Road, Palo Alto, CA, 94304); Dietrich, P. S. *Mutat Res* 66(3): 223-240; 1979.

Over 70 naturally occurring and synthetic flavonoids were screened for mutagenicity with tester strains TA1535, TA100, TA1537, TA1538, and TA98 in the Salmonella/mammalian microsome assay. Frameshift mutagenicity was confined to the flavonols (flavon-3-ols) in strains TA98, TA1537, and TA100. The two most mutagenic flavonols, quercetin (3,3',4',5,7-pentahydroxyflavone) and kaempferol (3,4',5,7-tetrahydroxyflavone), which produced 12 and 7 revertants/nanomole (nmol) in TA98, respectively, are also the most common flavonols occurring in plants. Other flavonols exhibited less activity (revertants/nmol): galangin (2.0), rhamnetin (0.45), kaempferide (0.24), fisetin (0.14), myricetin

(0.12), robinetin (0.06), and morin (0.05). All of these flavonols apparently were significantly activated by Aroclor 1254-induced rat liver microsome preparations (S9). However, subsequent study revealed that only those flavonols either lacking or possessing one B-ring OH group had an absolute requirement for microsomal activation. Alternatively, quercetin, with two B-ring OH groups, was not activated by microsomal enzymes, but by soluble (S100) enzymes from liver that are apparently constitutive and not subject to the usual chemical induction. The flavonol glycosides quercetrin (quercetin-3-O-rhamnoside), rutin (quercetin-3-O-rutinoside), and robinin (kaempferol-3-O-galactosidorhamnoside-7-O-rhamnoside) were nonmutagenic. They could, however, be activated by a variety of mixed glycosidases incorporated in the usual pour plate procedure. The most effective enzyme mixtures were obtained from rat cecal bacteria and from the snail *Helix pomatia*. (29 refs)

- 79-1925 Hormonal Influences on Chemical Carcinogenesis (Meeting Abstract).** (Eng) Chedid, A. (Chicago Medical Sch., Chicago, IL, 60612). *Fed Proc* 38(3, part 2): 1403; 1979. (no refs)

- 79-1926 Effects of Mycotoxin Combinations on Monooxygenase System and Adenosine Triphosphatase Activity in Neonatal Rats (Meeting Abstract).** (Eng) Siraj, M. Y. (Dept. Pharmacology and Toxicology, Univ. Mississippi Medical Center, Jackson, MS, 39216); Phillips, T. D.; Hayes, A. W. *Fed Proc* 38(3, part 1): 394; 1979. (no refs)

- 79-1927 Tissular Dynamics of the Oncofetal Markers α , Fetoprotein and γ -Glutamyl Transpeptidase in Rat Liver During Aflatoxin B₁ Induced Carcinogenesis.** (Eng) Kalengayi, M. M. (Laboratorium voor Histochemie en Cytochemie, Fakulteit Geneeskunde, Katholieke Universiteit Leuven, Leuven, Belgium); Gilli, J.; Desmet, V. J. In: *Prevention and Detection of Cancer. Part II. Detection. Vol. 1. High Risk Markers. Detection Methods and Management*. Nieburgs, H. E., ed. (New York: Marcel Dekker): 1299 pp.; 97-131; 1978.

To study the dynamics of α -fetoprotein (AFP) and γ -glutamyl transpeptidase (GGTP) in the liver during chemical hepatocarcinogenesis, male Wistar R rats were given aflatoxin B₁ (2.40 mg total dose by gastric intubation) according to three different schedules. AFP and GGTP were measured by indirect immunofluorescence (IF), double-immunodiffusion, countercurrent immunoelectrophoresis, and enzyme immunoassay (EI). During the first 10 wk of hepatocarcinogenesis, AFP levels in the drug-treated rats were significantly higher than those in the controls. The levels varied according

to the sensitivity of the detection method and the intoxication schedule. During this phase, AFP was produced by most of the transitional cells, renewed small hepatocytes, and regenerative areas, but not all of them. In contrast, GGTP activity was elevated in all proliferative areas and in every regenerative area. These changes disappeared when the carcinogen treatment was terminated. During the preneoplastic and neoplastic phases, AFP was detected only by EI and, to some extent, by IF, with only very rare nodules showing weak to moderate staining. The positive cells were arranged in trabeculae or they formed acini and tubules. Again, in contrast, a strong GGTP activity was observed in all nodules and hepatocarcinomas. The results indicate that both AFP and GGTP may be elevated in the liver before the appearance of overt hepatocarcinomas, but that GGTP is a far more sensitive marker of early, preneoplastic, and neoplastic changes than AFP. Both oncofetal markers may be useful for the study of preneoplastic and neoplastic conditions of the human liver. (61 refs)

79-1928 Aflatoxin in Peanuts: A New Approach to Consumer Protection. (Eng) Pusey, M. (Mars Ltd., Dundee Road, Slough Berks, England); Oliver, J. *Manuf Confect* 59(2): 45-47; 1979.

A new semimechanized method for analyzing aflatoxin levels in peanuts ("Aflamatic") allows faster analysis without lowering analytical standards. A 1-kg sample is taken from each ton of nuts and analyzed against a limit of 5 ppb total aflatoxins; the results for each 20-ton lot are dealt with by a strict decision-making network. The method provides a much cleaner extract, allows faster sample turnaround, and reduces the risk of cross-contamination. A schematic diagram of the Aflamatic process and a comparison of this process with two other methods are presented. (4 refs)

79-1929 Carcinogenesis by Dietary Nitrite in Experimental Animals (Meeting Abstract). (Eng) Asano, T. (Univ. Notre Dame, Notre Dame, IN, 46556). *Fed Proc* 38(3, part 2): 1451; 1979. (no refs)

79-1930 Hydrazine (Letter to Editor). (Eng) Roe, F. J. (4 Kings Road, Wimbledon, London SW19 8QN, England). *Ann Occup Hyg* 21(3): 323-326; 1978.

Data from 2/9 hydrazine manufacturers from five countries, although incomplete, provide evidence that past occupational exposures to hydrazine were not associated with any greatly increased risk of cancer. In the past, hydrazine vapor concentrations in ambient air in all nine companies were many times higher than the 0.1-ppm max that they currently claim to be achieving. Additional studies of workers in the nine companies is in progress. (12 refs)

79-1931 Carcinogenic Effects in the Syrian Golden Hamster of N-Methyl-N-formylhydrazine of the False Morel Mushroom *Gyromitra esculenta*. (Eng) Toth, B. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NE, 68105); Patil, K. *J Cancer Res Clin Oncol* 93(2): 109-121; 1979.

The tumorigenicity of N-methyl-N-formylhydrazine (NMNF: administered as a 0.0078% soln in the drinking water for life beginning at 6 wk of age) in Syrian golden hamsters was investigated. Survival rates for NMNF-treated and control hamsters were similar up to 1 yr, after which survival was unexpectedly greater among the treated animals. Nineteen of 50 treated females and 24/50 treated males developed liver tumors (25 hepatomas and 18 liver cell carcinomas), 24 females and 10 males developed malignant histiocytomas, 3 females and 8 males developed gallbladder tumors (7 papillary adenomas and 4 adenocarcinomas), and 1 female and 7 males developed tumors of the bile duct (2 cholangiomas and 6 cholangiocarcinomas). None of these tumors developed in the untreated control hamsters. Other tumors occurred in low incidence and could not be attributed to treatment. In view of the demonstrated carcinogenicity of NMNF, edible false morel mushrooms, which contain substantial amounts of the compound, should not be consumed by humans. (19 refs)

79-1932 Mathematical Models of Carcinogenesis and Tumor Growth in an Experimental Rat Colon Adenocarcinoma. (Eng) Maskens, A. P. (Cancer Res. Unit, Clinique Saint-Michel, B-1040 Brussels, Belgium). In: *Gastrointestinal Tract Cancer*. Lipkin, M.; Good, R. A., eds. (New York: Plenum Medical Book Co.): Sloan Kettering Institute Cancer Series 602 pp.; 361-384; 1978.

The mathematical treatment of data for experimental rat colon adenocarcinoma systems in which drug administration schedule and rate of tumor growth and yield are interrelated is presented. This treatment proved helpful in devising models of carcinogenesis and tumor growth patterns. The biological behavior of rat colon adenocarcinomas induced by weekly treatments with 1,2-dimethylhydrazine (DMH) is characterized by three main properties. These tumors are already truly invasive carcinomas when first recognized on microscopic examination of flat mucosa; thus, no benign polyp-cancer sequence is observed. Their av growth pattern is best fitted by a Gompertz function. The doubling time is short in small lesions but progressively increases as tumors enlarge. The number of tumors per colon rises as a nonlinear function of time. Based on these findings, and on the biochemical properties of DMH and related compounds, a two-step model of carcinogenesis is proposed. It implies that each DMH treatment induces a stable and transmissible change in a number of colon epithelial cells that thereafter will be at risk for a second mutationlike event responsible for initiating cancer growth. There are several possible human implications of this model. Although colorectal polyps progress toward cancer

with variable frequency according to histologic type, some carcinomas may also arise de novo in flat mucosa. The Gompertz growth model implies that the small and, consequently, most curable tumors represent an extremely brief stage as opposed to long-lasting, slowly growing large lesions. The multistep model of carcinogenesis implies that even minimal exposures to environmental carcinogens are significant, since they could contribute to the accumulation of permanently modified cells susceptible to further malignant changes. (72 refs)

- 79-1933 Cell Kinetics of Dimethylhydrazine(DMH)-induced Colonic Neoplasms and Their Adjacent Colonic Mucosa in the Mouse (Meeting Abstract).** (Eng) Chang, W. W. (Dept. of Anatomy, Mt. Sinai Sch. of Medicine of CUNY, New York, NY); Mak, K. M.; MacDonald, P. D. *Anat Rec* 193(3): 502; 1979. (1 ref)

- 79-1934 Immunogenicity of Chemically Induced Murine Colon Cancers.** (Eng) Belnap, L. P. (Dept. Surgery, Univ. Utah Medical Center, Salt Lake City, UT, 84111); Cleveland, P. H.; Colmerauer, M. E.; Barone, R. M.; Pilch, Y. H. *Cancer Res* 39(4): 1174-1179; 1979.

The antigenicity and immunogenicity of three colorectal carcinomas induced in female BALB/c mice by intrarectal injection of N-methyl-N-nitrosourea or by sc injection of 1,2-dimethylhydrazine (DMH) were studied. All tumors were readily transplanted. Two of these tumors (CT 26, an anaplastic carcinoma, and CT 51, a moderately well-differentiated mucinous adenocarcinoma) metastasized when transplants reached sufficient size. The third tumor (CT 36, a well-differentiated adenocarcinoma) rarely metastasized. All of the tumors were immunogenic in their strain of origin. CT 26 showed moderate immunogenicity, CT 51 weak immunogenicity. CT 36, however, was highly immunogenic, with an overall tumor incidence of 10% in immunized animals. Cross-protection experiments indicated that all tumors contained unique tumor-specific transplantation antigens. It is concluded that these three BALB/c colon carcinomas, especially CT 26 and CT 51, are excellent models for immunotherapy-chemoimmunotherapy experiments. (31 refs)

- 79-1935 Hydrazines as Mutagens in a Histidine-requiring Auxotroph of *Salmonella typhimurium*.** (Eng) Tosk, J. (American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595); Schmeltz, I.; Hoffmann, D. *Mutat Res* 66(3): 247-252; 1979.

The mutagenicity of several hydrazines (HZ's) and related compounds was tested in *Salmonella typhimurium* strain TA1530. In one series of assays, hydrazine sulfate was the most mutagenic compound tested, followed by acetylhydrazine

and 1,1-dimethylhydrazine, (DMH) Diacetylhydrazine was not mutagenic. The decrease in the number of revertants noted with higher doses of DMH may indicate an autoinhibition of mutagenicity. A similar effect in HZ mutagenicity was noted previously. Toxicity was dose-limiting for this series; ie, at higher doses, toxic effects could complicate the interpretation of the data. In another series of assays, N-aminomorpholine was the most potent HZ mutagen tested, even though it was considerably less toxic than most HZ's. Phenylhydrazine, however, was highly toxic and its mutagenicity was detected at doses that resulted in low survival of the tester organisms. The pharmaceuticals isoniazid and hydralazine were mutagenic, as were MH-30 and Royal MH, two commercial plant growth regulators formulated with maleic hydrazide. Pure maleic hydrazide was not mutagenic. The results also demonstrate the utility of strain TA1530 for determining the mutagenicity of diverse HZ's and related compounds. (13 refs)

- 79-1936 Lack of Effect of Butylated Hydroxytoluene on Dimethylhydrazine-induced Colon Carcinogenesis in Rats.** (Eng) Barbolt, T. A. (Center Experimental Pathology and Toxicology, Albany Medical Coll., Albany, NY, 12208); Abraham, R. *Experientia* 35(2): 257-258; 1979.

Male Sprague-Dawley albino rats were treated simultaneously with the antioxidant butylated hydroxytoluene (BHT: 6,600 ppm of diet) and the potent colon carcinogen dimethylhydrazine (DMH: 30 mg/kg/wk x 10 by stomach tube) to investigate the effect of these agents on colon carcinogenesis. The incidence and mean number of tumors per animal were similar to those in rats given DMH alone. Apparently, BHT did not exert any protective effect against colon carcinogenesis. (13 refs)

- 79-1937 Induction of Colonic Adenocarcinomas by 1,2-Dimethylhydrazine Intrarectally Administered in Rats.** (Eng) Markert, C. (Dept. Biochemistry, Vanderbilt Univ. Sch. Medicine, Nashville, TN); Rogers, L. W.; Chiu, J. F. *Digestion* 18(3/4): 261-265; 1978.

The carcinogenicity of intrarectally administered 1,2-dimethylhydrazine (DMH: 250 mg/kg given every third week for a total of 3 doses) was studied in Sprague-Dawley rats. The DMH-treated rats developed multiple epithelial tumors that exhibited the histologic appearance of polypoid, invasive adenocarcinomas similar to typical human colonic carcinomas. The tumors formed tubular glands lined by anaplastic columnar epithelium, a pattern that persisted in the invasive components of all tumors except one. This tumor exhibited bowel wall infiltration by randomly arranged individual tumor cells that contained copious amounts of mucin. This pattern was similar to that of human "gelatinous" or "colloid" adenocarcinomas, which are less common than the more differentiated tubular variety. The nonneoplastic

mucosa adjacent to the tumors generally exhibited increased nuclear size and decreased mucin production. (8 refs)

79-1938 Experimental Investigation on the Influence upon Chemical Carcinogenesis: 4th Communication. Influence of Different Diets on Colon Carcinogenesis by 1,2-Dimethylhydrazine in Sprague-Dawley Rats. (Eng) Schmahl, D. (Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany); Habs, M.; Wolter, S.; Kuenstler, K. *Z Krebsforsch* 93(1): 57-66; 1979.

The effect of diet on 1,2-dimethylhydrazine (DMH: 7 monthly sc injections of 30 mg/kg) carcinogenesis was studied in male and female Sprague-Dawley rats. Control rats were given a standard pelleted diet, and experimental animals were given a vegetarian diet (Diet 1), a high-fat diet (Diet 2), a high-cholesterol diet (Diet 3), or a high-carbohydrate (Diet 4). Animals given the standard diet and Diets 1-3 had a nearly 100% incidence of malignant tumors; animals given Diet 4 had a 33% malignant tumor incidence. Colon carcinomas were observed in a high percentage of animals given the standard diet (approx 63%) and Diet 1 (68%) in a lower percentage of animals given Diet 3 (53%) and Diet 2 (43%), and in comparatively few animals given Diet 4 (33%). Malignant kidney tumors were equally frequent in animals given Diets 1, 2, and 3 but much less frequent in those given Diet 4. Carcinomas of the ear duct and malignant hepatomas were found in approx equal numbers in animals of all groups. Nearly all animals given Diet 4 developed benign hepatomas and cholangiomas. Benign liver tumors were less frequent in animals given Diets 2 and 3 than in those given Diet 4 and least frequent in those given the standard diet and Diet 1. Animals given Diets 2 and 3 died earlier of malignant tumors than did those with malignant tumors given Diets 1 and 4; rats given Diet 1 had the longest survival times. Malignant tumors did not develop in animals that were not given DMH. Quantitative differences in carcinogen treatment may have been responsible for some of the differences observed in the DMH-treated animals. (10 refs)

79-1939 Effect of Dietary Ascorbic Acid on 1,2-Dimethylhydrazine-induced Colon Cancer in Rats (Meeting Abstract). (Eng) Reddy, B. S. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595); Hirota, N. *Fed Proc* 38(3, part 1): 714; 1979. (no refs)

79-1940 Influence of Dietary Agar and Tallow on Colon Carcinogenesis (Meeting Abstract). (Eng) Glauret, H. P. (Michigan State Univ., East Lansing, MI); Sander, C. H.; Sanger, V. L.; Bennink, M. R. *Fed Proc* 38(3, part 1): 714; 1979. (no refs)

79-1941 Effect of Refined Carbohydrates on Colon Cancer in the Albino Rat (Meeting Abstract). (Eng) Haller, J. K. (Univ. Illinois, Urbana, IL, 61801); Milner, J. A. *Fed Proc* 38(3, part 1): 714; 1979. (no refs)

79-1942 Investigations on the Carcinogenicity of Hydrazine Mycotoxins of an Edible Mushroom (Meeting Abstract). (Eng) Toth, B. (Eppley Inst. Res. Cancer, Univ. Nebraska, Omaha, NE, 68105); Nagel, D. *Fed Proc* 38(3, part 2): 1450; 1979. (no refs)

79-1943 Dichloroacetate a Mutagen (Letter to Editor)? (Eng) Herbert, V. (Bronx Veterans Admin. Hosp., Bronx, NY, 10468); Gardner, A.; Colman, N. *N Engl J Med* 300(11): 625; 1979.

The low-grade mutagenicity of dichloroacetate has been confirmed in the Ames test with *Salmonella typhimurium* strain TA98. (2 refs)

79-1944 Arylamidation and Arylation by the Carcinogen N-2-Fluorenylacetylamine: A Sensitive and Rapid Radiochemical Assay. (Eng) Fuchs, R. P. (Groupe de Biophysique, Institut de Biologie Moleculaire et Cellulaire du CNRS, 15 rue Descartes, 67084 Strasbourg Cedex, France). *Anal Biochem* 91(2): 663-673; 1978.

A rapid and sensitive radiochemical assay that allows determination of the percentage of N-2-fluorenylacetylamine (FA) covalently bound via arylamidation or arylation is described. N-Acetoxy-N-arylacetylamines, which are generally considered the ultimate carcinogenic forms of the corresponding N-arylacetylamine, react with cellular macromolecules (nucleic acids, proteins, etc) to give arylamidation or arylation adducts. The assay is based on the difference in stability under weak alkali hydrolysis conditions (0.1 N NaOH, 75 C, 2 hr) of the specifically ¹⁴C-labeled N-acetyl group of the FA residue linked to the macromolecule via arylamidation or arylation. Native DNA that has been reacted with ¹⁴C-labeled N-acetoxy-N-2-acetylaminofluorene exhibits 16% of the fluorene adducts linked to the bases via arylation. On the other hand, denatured DNA reacts with the fluorene derivative to give almost only arylamidation adducts. (21 refs)

79-1945 Comparison of Repair of DNA Damage Induced by Chemical Carcinogens, UV-Light and Gamma Rays Using ϕ X174 RF-DNA and Repair-Deficient *E. coli* Mutants (Meeting Abstract). (Eng) Taylor, W. D. (Pennsylvania State Univ., University Park, PA, 16802); Tsai, C. L.; Spitz, S.; McKee, R. H. *Fed Proc* 38(3, part 1): 622; 1979. (no refs)

- 79-1946 Formation and Removal of Specific Acetylaminofluorene-DNA Adducts in Mouse and Human Cells Measured by Radioimmunoassay.** (Eng) Poirier, M. C. (In Vitro Pathogenesis Section, NCI, NIH, Bldg. 37, Room 3A19, Bethesda, MD, 20014); Dubin, M. A.; Yuspa, S. H. *Cancer Res* 39(4): 1377-1381; 1979.

Rabbit antiserum prepared against N-(guanosin-8-yl)-acetylaminofluorene was used in a radioimmunoassay (RIA) to detect the formation and removal of C-8 adducts from the DNA of cultured cells exposed to N-acetoxy-2-acetylaminofluorene (N-Ac-AAF). The assay was able to quantitate both acetylated [N-(deoxyguanosin-8-yl)-acetylaminofluorene] and deacetylated [N-(deoxyguanosin-8-yl)aminofluorene] C-8 adducts between 0.5 and 5 picomoles (pmol), but the N² adduct, 3-(deoxyguanosin-N²-yl)acetylaminofluorene, was not detected below 160 pmol. By varying the proportions of acetylated and deacetylated C-8 adducts in the RIA, a series of standard curves was developed from which the relative proportion of each adduct could be determined in unknown mixtures. DNA from mouse epidermal cells and human skin fibroblasts exposed to N-Ac-AAF in culture contained only 3% and 5%, respectively, of the acetylated C-8 adduct. Quantitation by RIA of total C-8 adducts bound to DNA yielded values 25% lower than those of total carcinogen binding determined by radiolabeling. When removal of C-8 adducts was followed over a 23-hr carcinogen-free culture period, mouse and human cells removed 40% and 50%, respectively of bound acetylated and deacetylated C-8 adducts. Preliminary evidence suggests that the rate of removal of acetylated and deacetylated C-8 adducts is similar in each cell line, since the relative amount of each adduct was the same at 1 and 24 hr. The data indicate that RIA is a sensitive and specific means of measuring carcinogen-DNA adducts. (24 refs)

- 79-1947 Metabolism of 2-Aminofluorene and 2-Acetylaminofluorene to Mutagens by Rat Hepatocyte Nuclei.** (Eng) Stout, D. L. (Dept. Anatomic and Res. Pathology, M. D. Anderson Hosp. and Tumor Inst., Univ. Texas System Cancer Center, Houston, TX, 77030); Becker, F. F. *Cancer Res* 39(4): 1168-1173; 1979.

The ability of rat hepatocyte nuclei to metabolize 2-aminofluorene (AF) and 2-acetylaminofluorene (AAF) to mutagens was studied using the *Salmonella typhimurium* mutagenicity assay. Hepatocyte nuclei produced approx 1,260% more revertants with AF than with AAF; addition of the hepatic postmitochondrial fraction (S9) to the plate produced 1,640% more mutants with AF than with AAF. Pretreatment of rats with phenobarbital (PB) or methylcholanthrene (MC) altered metabolic activity in a manner that was unique for each fraction. PB pretreatment increased the nuclear activation of A and AAF to mutagens by 400% and 460% respectively. S9 from PB-treated rats increased the nuclear AF activation by 57% and AAF activation by 125%. MC pretreatment increased the activation of AF and AAF by 69%

and 375%, respectively. S9 activation of AAF was not altered by MC pretreatment, but AF activation was increased by 41%. In rats exposed to a carcinogenic regimen of AAF in the diet, nuclear activation of AF and AAF to mutagens was increased during the first 4 wk of feeding by 28% and 85%, respectively. However, after 16 wk on the AAF diet, nuclear activation of AF and AAF had diminished by 71% and 81%. These findings indicate that rat hepatocyte nuclei can activate AF and AAF mutagens. The data also suggest that the metabolic pathways for AF and AAF activation differ and that AF may play a prominent role in mutagenesis. (21 refs)

- 79-1948 Decreased Fidelity of DNA Polymerase Activity During N-2-Fluorenylacетamide Hepatocarcinogenesis.** (Eng) Chan, J. Y. (Dept. Pathology, Section Experimental Pathology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Becker, F. F. *Proc Natl Acad Sci USA* 76(2): 814-818; 1979.

The role of DNA synthesis during repair and the importance of DNA replication during cell division in the pathogenesis of the carcinogenic sequence led to an examination of the DNA polymerases during N-2-fluorenylacетamide (FAA)-induced hepatocarcinogenesis. α and β DNA polymerases (DNA nucleotidyltransferase; deoxynucleoside-triphosphate: DNA deoxynucleotidyltransferase) were isolated from nuclear and cytoplasmic fractions of the livers of male Sprague-Dawley rats fed FAA and from 24-hr regenerating liver. FAA was mixed with a standard synthetic diet at 0.06%. A feeding cycle consisted of 3 wk of FAA followed by 1 wk of regular meal; rats were treated with one to four cycles. The fidelity of polymerization of these enzymes was compared by determining the incorporation of noncomplementary deoxyribonucleoside triphosphates (misincorporation) on a poly(dA-dT).poly(dA-dT) template, with MnCl₂ and MgCl₂ as divalent cations. Initial studies indicated that the cytoplasmic α polymerases from carcinogen-exposed rat livers were strikingly error-prone, whereas the nuclear and cytoplasmic β polymerases retained their fidelity throughout the feeding cycles. The misincorporation was significantly accentuated by MnCl₂ compared with that obtained with MgCl₂. The products were sensitive to pancreatic DNase I digestion, indicating that the noncomplementary bases had been incorporated by the polymerization process. Nuclear α polymerase showed some degree of infidelity, but it was less than that of cytoplasmic α polymerase. (31 refs)

- 79-1949 Activation of the Carcinogen N-Hydroxy-2-acetylaminofluorene by Rat Liver Nuclei, Microsomes and Hog Liver Esterase Via Deacylation (Meeting Abstract).** (Eng) Floyd, R. A. (Oklahoma Medical Res. Foundation, Oklahoma City, OK, 73104); Steward, J. E.; Hampton, M. J.; Sridhar, R. *Fed Proc* 38(3, part 1): 658; 1979. (no refs)

- 79-1950 Acute Fine Structural Changes in Rat Hepatocytes Induced by a Single Large Dose of 2-Acetylaminofluorene.** (Eng) Flaks, B. (Dept. Pathology, Univ. Bristol Medical Sch., Bristol, England); Basley, W. A. *Virchows Arch [Cell Pathol]* 29(4): 309-320; 1979.

Electron microscopy was used to study the changes in hepatocytes from male rats given a single intragastric dose of 2-acetylaminofluorene (2-AAF: 600 mg/kg) and killed at intervals of up to 16 days after treatment. The reduction, disorganization, and degranulation of the granular endoplasmic reticulum, atrophy of the Golgi apparatus, nucleolar segregation, and lipid accumulation observed during the first 48 hr were consistent with the known activity of 2-AAF as an inhibitor of protein and RNA synthesis. Restoration of the normal morphology of the nucleoli and Golgi zones by day 5 indicated that at least partial recovery of RNA and protein synthesis had occurred. However, this recovery was accompanied by the peripheral displacement of cytoplasmic organelles by large perinuclear glycogen lakes. Cytoplasmic vacuolation of hepatocytes in the central and mid-zones of the lobules was most pronounced at day 7 when it was accompanied by scattered pyknosis. Restoration of an apparently normal liver histology was complete by day 14 after treatment. Ultrastructural changes that were observed at all stages of the experiment included alterations of granular endoplasmic reticulum and bile canaliculi, hypertrophy of the agranular endoplasmic reticulum, lipid accumulation, and increased abundance of autophagic vacuoles and residual bodies. These changes have been shown to occur during chronic exposure to 2-AAF, to become irreversible, and to be present in a variety of 2-AAF-induced hepatic cell neoplasms. The results indicate that the autoprotective effect of a high dose of a hepatotoxic agent is probably due to inhibition of protein synthesis and is analogous to cycloheximide protection. (48 refs)

- 79-1951 L-Ethionine Metabolism in Liver of Rats Fed DL-Ethionine and Other Hepatotoxins (Meeting Abstract).** (Eng) Brada, Z. (Papanicolaou Cancer Res. Inst., Miami, FL, 33101); Bulba, S. *Fed Proc* 38(3, part 2): 1404; 1979. (no refs)

- 79-1952 Effects of Type and Level of Dietary Lipids on Breast Carcinogenesis Induced by N-2-Fluorenylacetamide (Meeting Abstract).** (Eng) Fann, D. Y. (Texas Tech Univ., Lubbock, TX, 79409); Yang, S. P.; Felkner, I. C.; Sproat, H. F. *Fed Proc* 38(3, part 1): 864; 1979. (no refs)

- 79-1953 Protection by Butylated Hydroxytoluene Against Preneoplastic Nodular Development During the Continuous Feeding of 2-Acetylaminofluorene (AAF) (Meeting Abstract).** (Eng) McCay, P. B. (Oklahoma

Medical Res. Foundation, Oklahoma City, OK, 73104); King, M. M. *Fed Proc* 38(3, part 2): 1073; 1979. (no refs)

- 79-1954 Dominant-Lethal Assay of Selected Cytostatics.** (Eng) Sykora, I. (Res. Inst. Pharmacy and Biochemistry, Branch Inst. Pardubice-Rosice, 533 51 Pardubice, Czechoslovakia); Gandalovicova, D. *Neoplasma* 25(5): 523-533; 1978.

The effects of various cytostatic drugs on male fertility, abortions, dominant lethal mutations, and preimplantation losses of ova were studied in S strain mice. Male fertility was significantly reduced by trichlormethinium chloride (TS-160: 1 or 5 mg/kg ip, mercaptopurine (MP: 25 mg/kg/day x 14, ip), and β -4-n-pentoxybenzoyl- β -bromoacrylic acid (Penberol: 250 mg/kg/day x 14, po). Abortions and dominant lethal mutations in the fetuses were significantly higher among females mated with males treated with cyclophosphamide (12 or 15 mg/kg/day x 14, ip; or single dose of 100 mg/kg ip), TS-160 (5 mg/kg ip), sodium bromebrate (Cytembena; 25 mg/kg/day x 14, ip), or MP. Preimplantation losses of ova were increased following treatment of male mice with TS-160, Cytembena, or MP, and fetal resorptions were increased in frequency by cyclophosphamide, TS-160, Cytembena, γ , γ -bis-4-ethylphenyl- α , β -dibromoisocrotonic acid (Edikron), and MP. In the case of Cytembena (ip) and Edikron (po), resorption was seen after treatment with lower doses of drug (10 and 100 mg/kg/day x 14, respectively) but not with the higher doses (25 and 250 mg/kg/day x 14). (19 refs)

- 79-1955 The Effect of Glutathione and Other Thiol Compounds on the Generation of Mutagenic Metabolites of Cyclophosphamide (Meeting Abstract).** (Eng) Hales, B. F. (Dept. Pharmacology, Roche Developmental Pharmacology Unit, McGill Univ., Montreal, PQ, Canada). *Fed Proc* 38(3, part 1): 443; 1979. (no refs)

- 79-1956 Morphological Transformation of Hamster Embryo Cells by Cancer Chemotherapeutic Agents.** (Eng) Hirakawa, T. (Dept. Experimental Pathology, Cancer Inst., 1-37-1, Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan); Tanaka, M.; Takayama, S. *Toxicol Lett* 3(2): 55-60; 1979.

The abilities of various cancer chemotherapeutic agents to induce morphological transformation in hamster embryo cells were studied. The alkylating drug cyclophosphamide induced transformation at concentrations of 100-500 μ g/ml. Two other alkylating agents, N-methyl-bis(mesyloxypropyl)-amine-diphenyl-4, 4'-disulfonate and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), caused transformation at 0.5 μ g/ml, whereas carbazilquinone, methyl CCNU, and triethylenethiophosphoramidate were ineffective. Four an-

timetabolites, 6-mercaptopurine, 5-fluorouracil, cytosine arabinoside, and methotrexate, had a strong cytotoxic effect at 1 $\mu\text{g}/\text{ml}$ but did not induce morphologic transformation. The antitumor antibiotics actinomycin D, mitomycin C, and adriamycin induced transformation, whereas daunomycin, aclacinomycin A, and bleomycin were ineffective. The natural plant alkaloid vincristine caused slight transformation at 0.01 $\mu\text{g}/\text{ml}$. Most of the drugs that caused morphological transformation in vitro have been reported to be carcinogenic in vivo, whereas those that did not transform have not been shown to be carcinogenic. Thus, this in vitro assay system seems to be reliable for predicting chemical carcinogenicity. (17 refs)

- 79-1957 The Bovine Pancreas as a Model to Study Carcinogenesis (Meeting Abstract).** (Eng) Jones, R. T. (Dept. Pathology, Univ. Maryland Sch. Medicine, Baltimore, MD, 21201). *Lab Invest* 40(2): 294-295; 1979. (no refs)

- 79-1958 Syntheses of N-Alkyl-N-(hydroxy- or oxo-alkyl)nitrosamines Related to N-Butyl-N-(4-hydroxybutyl)nitrosamine, a Potent Bladder Carcinogen.** (Eng) Okada, M. (Tokyo Biochemical Res. Inst., Tokyo, Japan); Suzuki, E.; Iiyoshi, M. *Chem Pharm Bull (Tokyo)* 26(12): 3891-3896; 1978.

Thirteen N-alkyl-N-(hydroxy- or oxo-alkyl)nitrosamines structurally related to the potent bladder carcinogen N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) were synthesized, and their carcinogenicity in rats and mutagenicity for *Salmonella typhimurium* strain TA1535 were determined. Most were prepared by nitrosation of the corresponding N-alkyl-N-(hydroxyalkyl)amine, but those with an oxo group were prepared by chromium trioxide oxidation of the corresponding N-alkyl-N-(hydroxyalkyl)nitrosamine with a secondary hydroxyl group. BBN, N-methyl-N-(4-hydroxybutyl)nitrosamine, N-ethyl-N-(4-hydroxybutyl)nitrosamine, and N-propyl-N-(4-hydroxybutyl)nitrosamine selectively induced bladder cancer in the rats; N-amyl-N-(4-hydroxybutyl)nitrosamine induced papillomas of the bladder; N-butyl-N-(2-hydroxyethyl)nitrosamine and N-ethyl-N-(2-hydroxyethyl)nitrosamine induced hepatomas and papillomas of the esophagus; N-butyl-N-(3-hydroxybutyl)nitrosamine produced degenerative changes in the liver but no tumors; N-butyl-N-(3-oxobutyl)nitrosamine, N-butyl-N-(2-oxobutyl)nitrosamine, and N-butyl-N-(2-oxopropyl)nitrosamine produced hepatomas; and *t*-BBN produced no tumors. All compounds tested except *t*-BBN were mutagenic for *S. typhimurium* with metabolic activation. (17 refs)

- 79-1959 Syntheses of N-Alkyl-N-(α -acetoxyalkyl)nitrosamines, Model Compounds for Metabolical-**

ly Activated N,N-Dialkylnitrosamines. (Eng) Mochizuki, M. (Tokyo Biochemical Res. Inst., Tokyo, Japan); Anjo, T.; Okada, M. *Chem Pharm Bull (Tokyo)* 26(12): 3905-3908; 1978.

Nine new N,N-dialkylnitrosamines monosubstituted at the α -carbon with an acetoxy group were tested for mutagenicity to *Salmonella typhimurium* strain TA1535. When N-alkyl-N-(methoxymethyl)nitrosamines were refluxed in acetic acid, they were converted into N-alkyl-N-(acetoxyethyl)nitrosamines in low but satisfactory yield. The E-Z isomer ratios of the compounds were determined by nuclear magnetic resonance analysis. N-methyl-N-(acetoxyethyl)nitrosamine, N-ethyl-N-(acetoxyethyl)nitrosamine, N-propyl-N-(acetoxyethyl)nitrosamine (PAMN), *i*-PAMN, N-butyl-N-(acetoxyethyl)nitrosamine (BAMN), *i*-BAMN, *s*-BAMN, and N-butyl-N-(1-acetoxybutyl)nitrosamine were mutagenic for *S. typhimurium* without metabolic activation. *t*-BAMN was not mutagenic in this assay. (15 refs)

- 79-1960 Syntheses of N-Alkyl-N-(ω -carboxyalkyl)nitrosamines Related to N-Butyl-N-(3-carboxypropyl)nitrosamine, Principal Urinary Metabolite of a Potent Bladder Carcinogen N-Butyl-N-(4-hydroxybutyl)nitrosamine.** (Eng) Okada, M. (Tokyo Biochemical Res. Inst., Tokyo, Japan); Suzuki, E.; Iiyoshi, M. *Chem Pharm Bull (Tokyo)* 26(12): 3909-3913; 1978.

Fourteen N-alkyl-N-(ω -carboxyalkyl)nitrosamines related to N-butyl-N-(3-carboxypropyl)nitrosamine (BCPN) the principal urinary metabolite of the potent bladder carcinogen N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN), were prepared and tested for their carcinogenicity in rats and mutagenicity in *Salmonella typhimurium* strain TA1535. Most of the compounds were synthesized by permanganate oxidation of the corresponding N-alkyl-N-(ω -hydroxyalkyl)nitrosamines. The carcinogenicity of BCPN was as great as that of BBN, and the carcinogenicity of N-ethyl-N-(3-carboxypropyl)nitrosamine (ECPN), the principal urinary metabolite of N-ethyl-N-(4-hydroxybutyl)nitrosamine, was similar to that of its parent compound. Thus, compounds with 3-carboxypropyl chains are responsible for the organospecific action of compounds with 4-hydroxybutyl groups. N-butyl-N-(carboxymethyl)nitrosamine (BCMN), a minor metabolite of BBN, was noncarcinogenic. BCPN, ECPN, N-methyl-N-(3-carboxypropyl)nitrosamine, N-propyl-N-(3-carboxypropyl)nitrosamine, N-amyl-N-(3-carboxypropyl)nitrosamine, N-butyl-N-(2-carboxyethyl)nitrosamine, and N-butyl-N-(2-hydroxy-3-carboxypropyl)nitrosamine were mutagenic for *S. typhimurium*, whereas BCMN and *t*-BCPN were not. BCPN and its homologs with 3-carboxypropyl chains did not require metabolic activation for mutagenicity. (20 refs)

79-1961 Syntheses of N-(ω -Acetoxyalkyl and ω -Carbomethoxyalkyl)-N-(α -acetoxyalkyl)nitrosamines, Model Compounds for Possible Metabolically Activated N,N-Dialkylnitrosamines. (Eng) Mochizuki, M. (Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan); Anjo, T.; Okada, M. *Chem Pharm Bull (Tokyo)* 28(12): 3914-3919; 1978.

Nine new N-alkyl-N-(ω -acetoxyalkyl or ω -carbomethoxyalkyl)nitrosamines substituted at the α -carbon atom of the alkyl chain with an acetoxy group were synthesized, and they were tested for mutagenicity to *Salmonella typhimurium* strain TA1535 and other bacterial strains and for DNA-modifying effects in the *rec* assay. The compounds were N-(2-acetoxyethyl)-N-(acetoxymethyl)nitrosamine, N-(3-acetoxypropyl)-N-(acetoxymethyl)nitrosamine, N-(4-acetoxybutyl)-N-(acetoxymethyl)nitrosamine, N-(carbomethoxymethyl)-N-(acetoxymethyl)nitrosamine, N-(2-carbomethoxyethyl)-N-(acetoxymethyl)nitrosamine, N-(3-carbomethoxypropyl)-N-(acetoxymethyl)nitrosamine, N-(carbomethoxymethyl)-N-(1-acetoxybutyl)nitrosamine, N-(2-carbomethoxyethyl)-N-(1-acetoxybutyl)nitrosamine, N-(2-carbomethoxymethyl)-N-(1-acetoxybutyl)nitrosamine, and N-(3-carbomethoxypropyl)-N-(1-acetoxybutyl)nitrosamine. All nine compounds were shown to be more or less effective in the test assays. In the mutagenicity assay, they were active without metabolic activation. (19 refs)

79-1962 Maintenance in Organ Culture of Mouse Bladder Urothelium and Response to Bladder Carcinogens (Meeting Abstract). (Eng) Telang, N. T. (American Health Foundation, Naylor Dana Inst., Valhalla, NY, 10595); Hecht, S. S.; Williams, G. M. *Fed Proc* 38(3, part 2): 1074; 1979. (1 ref)

79-1963 Formation of N-Nitrosamines from Secondary Amines and Nitrite by Resting Cells of *Escherichia coli* B. (Eng) Kunisaki, N. (Dept. Enzymology, Res. Inst. for Chemobiodynamics, Chiba Univ., 1-8-1 Iohana, Chiba, Japan); Hayashi, M. *Appl Environ Microbiol* 37(2): 279-282; 1979.

Conditions for the formation of dimethylnitrosamine (DMNA) from dimethylamine (DMA) and nitrite by resting cells of *Escherichia coli* B were studied. The pH optimum for the microbial formation of DMNA was 8.0, vs a pH optimum of 3.4 (determined previously) for the chemical formation of DMNA. The formation of DMNA by *E. coli* B was proportional to incubation time and cell concentration, it did not occur when the cells were boiled before incubation, and it occurred equally well when piperidine replaced DMA as substrate. Lineweaver-Burke plots were linear up to 0.2 M DMA or 0.1 M nitrite. The reaction was inhibited at concentrations higher than 0.4 M DMA or piperidine or 0.12 M nitrite. The apparent K_m values were 0.12 M for DMA, 0.07

M for nitrite, and 0.15 M for piperidine. Cells disrupted by a French pressure cell were incapable of nitrosating DMA or piperidine, as were the supernatant and debris fractions resulting from fractionation of these cells. The results suggest that the formation of N-nitrosamine by resting cells of *E. coli* B depends on their enzyme activities. (14 refs)

79-1964 Evidence of Carcinogen-induced Replication of Partially-repaired DNA in Target Cells During Nitrosamine Carcinogenesis. (Eng) Stewart, B. W. (Sch. Pathology, Univ. New South Wales, Box 1, Kensington, New South Wales, Australia 2033); Brian, M. J. *Eur J Cancer* 15(2): 251-256; 1979.

Chromatography on benzoylated diethylaminoethylcellulose (BD cellulose) was used to study the damage and repair of rat kidney DNA following exposure of rats to renal carcinogens. Female Wistar rats were inoculated ip with dimethylnitrosamine (DMN: 0-40 mg/kg) or diethylnitrosamine (DEN: 0-200 mg/kg). DEN increased the fraction of renal DNA that bound to BD cellulose and subsequently eluted with 1.8% caffeine. The increase was proportional to DEN dose and was highest (59%) 24 hr after treatment. The amount of caffeine-eluted renal DNA was also approx proportional to DMN dose, and the amount eluted 4 hr after DMN administration was increased more than twofold in animals maintained on a glucose-sucrose diet. The max level of caffeine-eluted DNA was obtained 24 hr after treatment with 40 mg/kg DMN, and it was 140% greater than that in control animals. The level decreased slightly between 2 and 3 days after administration, and then it rose sharply at 4 days. After the fifth day, the level decreased again, and on day 7 it was approx 25% greater than the control level. The increase on day 4 may have been due to DMN-induced proliferative activity in the kidney. The replication of cells containing persistent carcinogen-induced damage may play an important role in this tumor induction system. (36 refs)

79-1965 Possible Formation of Nitrosamine in Guinea Pigs Following Exposure to NO₂ and Dimethylamine (Meeting Abstract). (Eng) Chaudhari, A. (Wayne State Univ., Detroit, MI, 48201); Dutta, S. *Fed Proc* 38(3, part 1): 369; 1979. (1 ref)

79-1966 Sequential Quantitative Studies on Hyperplastic Nodules in the Liver of Rats Treated with Carcinogenic Chemicals. (Eng) Tatematsu, M. (First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan); Murasaki, G.; Nakanishi, K.; Miyata, Y.; Shinohara, Y.; Ito, N. *Gann* 70(1): 125-130; 1979.

The induction of hyperplastic liver nodules in male Fischer

rats by a single dose of diethylnitrosamine (DEN, 200 mg/kg ip) followed 2 wk later by 10 wk of treatment with N-(2-fluorenyl)acetamide (2-FAA, 0.02% of the diet), the α -isomer of 1,2,3,4,5,6-hexachlorocyclohexane (α -BHC, 0.10% of the diet), or phenobarbital (PB, 0.05% of the diet) was studied. The animals were subjected to partial hepatectomy during the second week of carcinogen feeding. Treatment with DEN followed by 2-FAA, α -BHC, or PB resulted in the appearance of small foci on the surface of the liver within 4-8 wk. The cells in these nodules had a foamy, usually basophilic, cytoplasm and vesicular nuclei with prominent nucleoli. The av cross-sectional areas of the nodules increased during treatment. From week 6, significantly higher percentages of hyperplastic nodules per unit area of liver were found in all treated groups compared with the untreated controls. From week 8, significantly more nodules were found in the treated groups compared with the control group. Continuous administration of α -BHC or PB alone for 12 wk and partial hepatectomy did not induce hyperplastic nodules. Continuous administration of 2-FAA induced fewer nodules than did treatment with DEN followed by 2-FAA. (17 refs)

79-1967 Ultrastructure of Spontaneous Hepatic Neoplasms and of Neoplasms Induced by Diethylnitrosamine or Dieldrin in the C₃H Mouse (Meeting Abstract). (Eng) Ruebner, B. H. (Sch. Medicine, Univ. California, Davis, CA, 95616); Gershwin, M. E.; Hsieh, L.; Dunn, P. *Fed Proc* 38(3, part 2): 1451; 1979. (no refs)

79-1968 Cell Kinetics of Hepatocytes During the Preneoplastic Period of Diethylnitrosamine-induced Liver Carcinogenesis. (Eng) Rabes, H. M. (Inst. Pathology, Univ. Munich, Thalkirchnerstrasse 36, 8000 Munich 2, W. Germany); Szymkowiak, R. *Cancer Res* 39(4): 1298-1304; 1979.

Cell kinetic parameters of normal and preneoplastic enzyme-deficient hepatocytes were determined in male Wistar rats continuously fed diethylnitrosamine (DEN; 5mg/kg/day in drinking water). The fraction of labeled mitoses of all hepatocytes as a function of time after a single injection of ³H-thymidine revealed an increment in T-S from 9.6 to 11.6 hr at 20 and 118 days of DEN feeding, respectively. T-G₂ remained constant at 4 hr. The fraction of proliferating cells with a T-C < 40 hr increased from < 20% to 74% at 20 and 118 days, respectively. ATPase-deficient areas (islands) increased in cell number during the preneoplastic period, going from ≤ 25 cells/section at 30 days of feeding to ≤ 400 cells at 90 days and $\leq 5,000$ cells at 120 days. The labeling index after a single ³H-thymidine injection remained at 3%-4% until 90 days and then increased. The T-S's in enzyme-deficient (E-D) islands were 7.4 and 6.7 hr at 90 and 120 days, respectively. When the islands were evaluated as a function of size, a decrease of T-S was found in the larger E-D areas. E-D preneoplastic cells showed a proliferative advantage over nor-

mal liver cells. The E-D population responded to partial hepatectomy by an increase in DNA-synthesizing cells that was higher than that in the surrounding tissue. Partial hepatectomy shortened the preneoplastic period significantly when performed early after the start of DEN feeding. The proliferative advantage of a preneoplastic population may be explained in part by the increasing resistance of these cells against the toxic action of the carcinogen. (42 refs)

79-1969 Tumorigenicity of the Dihydrodiols of Dibenz(a,h)anthracene on Mouse Skin and in Newborn Mice. (Eng) Buening, M. K. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche, Inc., Nutley, NJ, 07110); Levin, W.; Wood, A. W.; Chang, R. L.; Yagi, H.; Karle, J. M.; Jerina, D. M.; Conney, A. H. *Cancer Res* 39(4): 1310-1314; 1979.

Dibenz(a,h)anthracene (DBA) and its three metabolically possible trans-dihydrodiols, trans-3,4-dihydroxy-3,4-dihydrobenz(a,h)anthracene (DBA 3,4-dihydrodiol), trans-1, 2-dihydroxy-1, 2-dihydrodibenz (a,h) anthracene (DBA 1,2-dihydrodiol), and trans-5,6-dihydroxy-5,6-dihydrodibenz(a,h)anthracene (DBA 5,6-dihydrodiol), were tested for tumorigenic activity on mouse skin and in newborn mice. A single topical application of 10-160 nanomoles (nmol) of the test compound to female CD-1 mice was followed 7 days later by application of 12-O-tetradecanoylphorbol-13-acetate (16 mol/200 μ g acetone, 2x/wk for 25 wk). DBA and DBA 3,4-dihydrodiol had the same tumorigenicity on mouse skin and were far more potent as skin tumor initiators than the 1,2- or 5,6-dihydrodiols. trans-3,4-Dihydroxy-1,2,3,4-tetrahydrodibenz(a,h)anthracene (DBA H₁-3,4-diol), which is saturated at position 1,2, was considerably less tumorigenic than DBA 3,4-dihydrodiol. Swiss-Webster BLU/Ha Icr strain mice were given 10, 20, and 40 nmol or 60, 120, and 240 nmol ip of the test compound on days 1, 8, and 15 of life (total doses 70 and 420 nmol respectively) and killed when 25-29 wk old. Less than 20% of control mice or mice treated with the 1,2- or 5,6-dihydrodiols developed pulmonary tumors. In mice treated with a total of 70 or 420 nmol of DBA, 88% and 100%, respectively, developed pulmonary tumors. In mice treated with 70 or 420 nmol of DBA 3,4-dihydrodiol, 83% and 99%, respectively, developed pulmonary tumors. Hepatic neoplastic nodules were found in 42% of the male mice treated with 420 nmol of DBA 3,4-dihydrodiol but not in female mice or in mice given any other treatment. These results support the prediction of the bay region theory that DBA 3,4-dihydrodiol is a proximate carcinogenic metabolite of DBA. (31 refs)

79-1970 Nitrosamine Activation by Hamster Pancreas and Revertant Mutation of *S. typhimurium* TA-1535 (Meeting Abstract). (Eng) Scarpelli, D. G. (Dept. Pathology, Northwestern Univ., 303 E. Chicago Ave., Chicago, IL. 60611); Rao, M. S.; Hollenberg, P. F. *Fed Proc* 38(3,

part 2): 1073; 1979. (no refs)

79-1971 Hepatic RNA Synthesis in Rats Treated with Ethylene Thiourea (Meeting Abstract). (Eng)

Austin, G. E. (Dept. Pathology, Univ. California at Los Angeles, Los Angeles, CA, 90024); Moyer, G. H. *Fed Proc* 38(3, part 2): 1404; 1979. (no refs)

79-1972 Conformational Membrane Changes in Neoplastic Urothelial Cells as Affected by 13-cis-Retinoic Acid (Meeting Abstract). (Eng) Tannenbaum, M.

(Div. Urothology, Dept. Pathology, Columbia Univ., New York, NY); Tannenbaum, S.; Trown, P. W. *Lab Invest* 40(2): 287; 1979. (no refs)

79-1973 Comparison of Mutagenicity, Antitumor Activity, and Chemical Properties of Selected Nitrosourea and Nitrosoamides. (Eng) Brundrett, R. B.

(Pharmacology Lab., Johns Hopkins Oncology Center, Baltimore, MD, 21205); Colvin, M.; White, E. H.; McKee, J.; Hartman, P. E.; Brown, D. L. *Cancer Res* 39(4): 1328-1333; 1979.

Several nitrosoureas and nitrosoamides were tested for mutagenicity in *Salmonella typhimurium*, in vitro cytotoxicity, in vivo toxicity, and antitumor activity against murine L1210 leukemia. In aqueous soln, N-(2-chloroethyl)-N-nitrosourea (CENU), N-nitroso-N-(2-chloroethyl)acetamide (CENA), N-methyl-N-nitrosourea (MNU), and N-methyl-N-nitrosoacetamide (MNA) decomposed by similar mechanisms (probably via diazohydroxide intermediate) to give analogous products. Of 10 compounds tested, only 3 nitrosoureas (MNU, CENU, and N,N'-bis(2-chloroethyl)-N-nitrosourea], showed a significant antitumor effect (> 20% increase in the life-span of treated animals). Although the compounds tested were toxic to the whole animal, the chloroethylnitrosoureas were significantly more toxic than the other compounds, except CENA. In the three cases in which pairs of analogs of equal chain length were tested for mutagenicity [MNA and MNU, CENA and CENU, and N-nitroso-N-(n-propyl)acetamide and N-nitroso-N-(n-propyl)urea] the nitrosourea was lower in mutagenic activity than the corresponding nitrosoamide. These findings indicate that in this series there is a dissociation of antitumor and mutagenic effects. The determination of the biochemical basis for this dissociation should lead to a better understanding of the chemical and biochemical determinants of antitumor effects vs mutagenicity (and, presumably, carcinogenicity). (40 refs)

79-1974 Characterization of Malignant Cell Populations in MNU-induced Leukaemia of Mice. (Eng)

Baines, P. (Paterson Lab., Withington, Manchester M20 9BX, England); Dexter, T. M.; Schofield, R. *Leuk Res* 3(1): 23-28; 1979.

The nature of methylnitrosourea (MNU)-susceptible target cells in intact and thymectomized (Th-x) BDF1 (C57BL/6 x DBA/2J F1) mice with MNU-induced (50 mg/kg iv) leukemias was studied. Th-x greatly prolonged the induction time and reduced the yield of MNU-induced leukemias. Leukemias of intact mice were commonly associated with thymic enlargement and with enlargement and leukemic infiltration of the spleen, lymph nodes, and liver. MNU-treated Th-x mice usually presented with enlarged mesenteric lymph nodes and/or enlarged spleens that were occasionally hemorrhagic. The leukemias of intact mice were more readily passaged to syngeneic recipients than those of Th-x mice. The leukemias in all cases were often comprised of undifferentiated blasts and lymphocytes. The enlarged, leukemic organs of the intact mice frequently contained large numbers of cells with Thy-1 + (T-cell) markers, whereas substantial proliferation of a Thy-1-, immunoglobulin-positive (Ig +) population was apparent in the affected organs of half of the Th-x mice. Half of the remaining leukemias in the Th-x animals were Ig + (B-cell) lymphomas and half showed low-intensity staining from both Thy-1 and Ig. Implants of neonatal thymus into syngeneic Th-x mice after MNU treatment did not reduce the induction time or increase the incidence of leukemias. Thymic lymphomas apparently developed only when the thymus had been directly exposed to MNU. Irradiation had no effect on MNU leukemogenesis. Leukemias of intact and Th-x mice do not appear to arise from a common target cell. In fact, MNU-induced thymic lymphoma arises from an intrathymic target population. (15 refs)

79-1975 Morphogenesis of Pancreatic Carcinoma in Organ-cultured Embryonic Rat Pancreas Induced by Methylnitrosourea (MNU) (Meeting Abstract). (Eng)

Parsa, I. (State Univ. New York, Downstate Medical Center, Brooklyn, NY, 11203). *Fed Proc* 38(3, part 2): 1451; 1979. (no refs)

79-1976 Gastric Cancer Etiology: A Biochemical Hypothesis. (Eng) Lilienfeld, D. E.

(Dept. Epidemiology, Johns Hopkins Univ., Sch. Hygiene and Public Health, 615 N. Wolfe St., Baltimore, MD, 21205); Gargliano, C. F. *Med Hypotheses* 5(1): 145-151; 1979.

A two-stage biochemical model for the etiology of intestinal-type gastric cancer is proposed. The model postulates that the gastric mucosal barrier is biochemically pierced as a result of chemical interactions between the mucoproteins and mucopolysaccharides of the barrier and ingested polysaccharides (starches). This would allow the growth of gastric flora that could produce carcinogenic nitrosamines and/or nitrosamides. Evidence presented in favor of the model includes

the observation that a decline in starch consumption has preceded a decline in gastric cancer mortality in both the US and Japan. (35 refs)

79-1977 Effects of Dietary Administration of Cheno-deoxycholic Acid on Induced Colon Cancer in Rats (Meeting Abstract). (Eng) Sarwal, A. N. (New York Univ. Medical Center, Public Health Res. Inst., New York, NY, 10016); Raicht, R. F.; Cohen, B. I.; Takahashi, M.; Faz-zini, E. *Fed Proc* 38(3, part 1): 864; 1979. (no refs)

79-1978 Effects of Phenobarbital (PB), Pregnenolone-16 α -carbonitrile (PCN) and 3-Methylcholanthrene (MC) on the Distribution of NADPH-Cytochrome c (Cytochrome P-450) Reductase in Rat Liver (Meeting Abstract). (Eng) Taira, Y. (Dept. Pharmacology, Univ. Iowa, Iowa City, IA, 52242); Greenspan, P.; Kapke, G.; Redick, J.; Baron, J. *Fed Proc* 38(3, part 1): 691; 1979. (no refs)

79-1979 Effects of Phenobarbital and 3-Methylcholanthrene on the Distributions of Cytochromes P-450 in Rat Liver (Meeting Abstract). (Eng) Baron, J. (Dept. Pharmacology, Univ. Iowa, Iowa City, IA, 52242); Redick, J. A.; Kapke, G. F.; Guengerich, F. P. *Fed Proc* 38(3, part 1): 660; 1979. (1 ref)

79-1980 Immunological Comparison of Hepatic and Extrahepatic Cytochromes P-450. (Eng) Guengerich, F. P. (Dept. Biochemistry, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232); Mason, P. S. *Mol Pharmacol* 15(1): 154-164; 1979.

Antibodies to two apparently homogenous cytochromes P-450 prepared from the liver microsomes of phenobarbital (PB) and 3-methylcholanthrene (3-MC)-treated male Sprague-Dawley rats were used to examine the similarity between hepatic and extrahepatic P-450's from PB- and 3-MC-treated rats. At least one microsomal preparation from liver, lung, kidney, testis, spleen, heart, small intestine, colon, stomach, and brain showed a visible reaction with one of the liver P-450 antibodies in double-diffusion analyses. The benzo(a)pyrene hydroxylase or 7-ethoxycoumarin O-deethylase activity of microsomes from each tissue except spleen and colon was inhibited by the liver P-450 antibodies, the degree of inhibition being dependent on the substrate, antibody, and drug treatment of the rats from which the microsomes were prepared. In general, microsomes from 3-MC-treated rats were inhibited most readily by antibody to cytochrome P-450 isolated from the liver microsomes of 3-MC-treated rats; the same was true for PB induction, although many exceptions were noted. The results indicate that hepatic and extrahepatic

P-450's are, in general, similar as judged by immunological techniques. (36 refs)

79-1981 Dose-dependent Fate of 1,4-Dioxane in Rats. (Eng) Young, J. D. (Toxicology Res. Lab., Dow Chemical Co., 1803 Building, Midland, MI, 48640); Braun, W. H.; Gehring, P. J. *J Toxicol Environ Health* 4(5/6): 709-726; 1978.

A pharmacokinetic study showed that the fate of 1,4-dioxane in rats is markedly dose-dependent because of their limited capacity to metabolize dioxane to β -hydroxyethoxyacetic acid. Correlation of the dose-dependent fate of dioxane with the results of toxicological studies in rats supported the conclusion that there is an apparent threshold for the toxic effects of dioxane that coincides with saturation of the metabolic pathway for its detoxification. (28 refs)

79-1982 Results of a Two-Year Chronic Toxicity and Oncogenicity Study of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in Rats. (Eng) Kociba, R. J. (Toxicology Res. Lab., Health and Environmental Res., Dow Chemical U.S.A., Midland, MI, 48640); Keyes, D. G.; Beyer, J. E.; Carreon, R. M.; Wade, C. E.; Dittenber, D. A.; Kalnins, R. P.; Frauson, L. E.; Park, C. N.; Barnard, S. D.; Hummel, R. A.; Humiston, C. G. *Toxicol Appl Pharmacol* 46(2): 279-303; 1978.

Groups of Sprague-Dawley rats were maintained for up to 2 yr on diets supplying 0.1 μ g [2,193 parts per trillion (ppt)], 0.01 μ g (208 ppt), or 0.001 μ g (22 ppt) of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)/kg/day. A dose of 0.1 μ g/kg/day increased the incidence of hepatocellular carcinomas (female only) and squamous cell carcinomas of the lung, hard palate/nasal turbinates, and tongue, but it decreased the incidence of tumors of the pituitary, uterus, mammary gland, pancreas, and adrenal gland compared with controls. Morphological changes in hepatic, lymphoid, respiratory, and vascular tissue were seen by light and electron microscopy. The primary hepatic ultrastructural changes at this high dose level was proliferation of the rough endoplasmic reticulum. Other toxic effects included increased mortality, decreased wt gain, increased urinary excretion of porphyrins and δ -aminolevulinic acid, slight depression of erythroid parameters, and increased serum activities of alkaline phosphatase, γ -glutamyl transferase, and glutamic-pyruvic transaminase. Rats treated with 0.01 μ g/kg/day generally showed a lesser degree of toxicity, and treatment with the lowest dose caused no effects of toxicologic importance. Liver and fat samples collected at terminal necropsy (after 2 yr of treatment) of rats of the three dosage groups contained 24,000 and 8,100, 5,100 and 1,700, and 540 and 540 ppt of TCDD, respectively. It is concluded that doses sufficient to induce severe toxicity increased the incidence of some types of neoplasms in rats and reduced the incidence

of others. There was no increase in neoplasms in rats receiving TCDD doses that induced slight or no manifestations of toxicity. (9 refs)

79-1983 Different Effect of 2,3,7,8-Tetrachlorodibenzo-p-dioxin on Glucuronide Conjugation of Various Aglycones. Studies in Wistar and Gunn Rats. (Eng) Aitio, A. (Dept. Physiology, Univ. Turku, Kiinamyllynkatu 10, SF-20520 Turku 52, Finland); Parkki, M. G.; Marniemi, J. *Toxicol Appl Pharmacol* 47(1): 55-60; 1979.

The effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD: 20 µg/kg intragastrically) on the activity of uridine diphosphate-glucuronosyltransferase (UDPGT) in the liver and kidney was studied in adult Gunn (G), Wistar (W), and W-G hybrid rats. In the W rats, TCDD caused an 8-fold increase in liver UDPGT activity toward 4-methylumbelliferone (4-MU), a 2-fold increase in kidney UDPGT toward 4-MU, an 8-fold increase in the liver conjugation of o-aminophenol (o-AP), and p-nitrophenol (p-NP), a 2-fold increase in the renal conjugation of o-AP and p-NP, and no effect on the hepatic or renal conjugation of bilirubin. In the W-G hybrids, TCDD caused a 5-fold increase in the liver conjugation of 4-MU, a 2-fold increase in the kidney conjugation of 4-MU, a 7-fold increase in the liver conjugation of o-AP and p-NP, and a 2-fold increase in the kidney conjugation of o-AP and p-NP; there was no effect on the activity of UDPGT toward bilirubin. TCDD had no effect on the hepatic or renal conjugation of any aglycone in the Gunn rats. Diethylnitrosamine (15 mM in the in vitro incubation mixture) had no effect on the conjugation of 4-MU, nonsignificantly decreased the conjugation of bilirubin, markedly increased the hepatic activity of UDPGT in untreated (especially G) rats, and had no effect on the hepatic or renal conjugation of o-AP or p-NP in the TCDD-treated rats. (24 refs)

79-1984 Comparison of Phenobarbital- and Carcinogen-induced Aldehyde Dehydrogenases in the Rat. (Eng) Marselos, M. (Dept. Physiology, Univ. Kuopio, Kuopio 10, Finland); Torronen, R.; Koivula, T.; Koivusalo, M. *Biochim Biophys Acta* 583(1): 110-118; 1979.

The induction of liver aldehyde dehydrogenase (AD) activity by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, 80 µg/kg, ip), phenobarbital (PB, 1 mg/ml in the drinking water for 7 days), 2-acetamidofluorene (AAF, 0.02% of the diet for 3 mo), and various carcinogenic agents was studied in Sprague-Dawley (chronic AAF treatment only) and Wistar/AF/Han/Mol/(Han 67) rats. Substrain rr of the latter strain showed no induction of liver or intestinal postmitochondrial fraction AD activity after PB, whereas both activities were increased (7- and 2-fold, respectively) in substrain RR rats. TCDD caused a 40-fold increase in liver AD and a significant increase in serum AD in both strains. Acute administration of AAF or urethan (100

mg/kg intragastrically for 4 days) had no effect on the liver or small intestinal AD of rr rats, whereas a 40-fold increase was seen after 3-methylcholanthrene (100 mg/kg), a 30-fold increase after benzo(a)pyrene (100 mg/kg), and a 2-fold increase after chrysene (200 mg/kg). The latter three compounds were also given intragastrically for 4 days. Chronic AAF administration resulted in a 15-fold increase in liver AD. The activities induced by TCDD and the carcinogenes showed similar isoelectric focusing patterns in gel slabs and similar mol wts, as determined by gel chromatography. These activities were clearly differentiated from the normal cytoplasmic activity and from that induced by PB. (19 refs)

79-1985 Inhibitory and Mutagenic Effects of Sodium Nitroprusside and Its Adenine Complex on *Escherichia coli*. (Eng) Szilagyi, I. (Inst. Biology, Univ. Medical Sch., P.O. Box 23, H-4012 Debrecen, Hungary); Vitalis, S. *Acta Microbiol Acad Sci Hung* 25(4): 285-289; 1978.

Sodium nitroprusside and its adenine complex decreased the growth rate of exponentially growing *Escherichia coli* cultures, and the adenine complex was actually bactericidal. The adenine complex failed to induce base-pair substitutions in *E. coli* in mutagenicity experiments; however, these experiments did not exclude the possibility of weak mutagenicity or the induction of frameshift mutations. (5 refs)

79-1986 A Model for 2-Aminopurine Mutagenesis: 2-Aminopurine-Hydroxymethylcytosine Base Pair Intermediates in T4 Bacteriophage. (Meeting Abstract). (Eng) Hopkins, R. (Univ. Southern California, Los Angeles, CA, 90007); Goodman, M. F. *Fed Proc* 38(3, part 1): 489; 1979. (no refs)

79-1987 Comparative Carcinogenicity of Vinyl or Imine Bridged 5-Nitrofurans in the Rat (Meeting Abstract). (Eng) Erturk, E. (Dept. Human Oncology, Univ. Wisconsin Center Health Sciences, Madison, WI, 53792); Headley, D. B.; Bryan, G. T. *Fed Proc* 38(3, part 2): 1403; 1979. (no refs)

79-1988 Azide Mutagenesis in Gram-negative Bacteria. Reversion of the Mutagenic Effect by L-Cysteine. (Eng) Ciesla, Z. (Inst. Biochemistry and Biophysics, Polish Acad. Sciences, ul. Rakowiecka 36, 02-532 Warsaw, Poland); Filutowicz, M. *Mutat Res* 66(3): 301-305; 1979.

Several experiments were conducted to determine the mechanism of the mutagenic action of azide (AZ). Prior inhibition of DNA synthesis with nalidixic acid (10 µg/ml) did not significantly alter the mutagenicity of AZ (3 mM) in *Sal-*

monella typhimurium strain TA1530, which suggests that DNA replication is not required for AZ mutagenicity. In a search for the metabolic pathway that may be involved in the activation of AZ to the ultimate mutagen (UM), the effect of L-cystine or L-cysteine (each, 0.5 mM) on the mutagenicity of 0.02 mM AZ in strain 1530 was determined. Both amino acids reduced the number of mutations to near control levels. This effect was specific, as other compounds containing the SH group (cysteamine and mercaptoethanol) did not affect the mutation rates. The possibility that AZ may be a substrate to one of the L-cysteine biosynthetic enzymes and that repression of the enzyme by L-cystine would result in a decreased rate of AZ metabolism (and, thus, UM concentration) was also tested. The mutagenicity of AZ in *S. typhimurium* strain TK1825 (which carries the *cysB1532* mutation plus *uvrB* and *hisG46*) was reduced significantly by L-cystine. The mutagenicity of AZ was much lower in TK1825 than in TA1530, an expected result if the cellular concentration of L-cysteine in TK1825 is higher than that in wild-type bacteria. The results do not necessarily mean that AZ is not metabolized by L-cystine enzymes that are repressed by growth in the presence of L-cystine. Two other possible explanations of the effect of L-cystine on AZ mutagenesis are given: cysteine desulfhydrase could be involved in inactivation of the UM, or L-cysteine and L-cystine may react with the UM. (18 refs)

- 79-1989 **Morphologic Response of Cultured Rat Pancreatic Ducts to Carcinogens (Meeting Abstract).** (Eng) Holmquist, D. R. (Dept. Biological Sciences, Univ. New Orleans, New Orleans, LA, 70122); Whelan, J. F.; Githens, S.; Ruby, J. R. *Lab Invest* 40(2): 260-261; 1979. (no refs)

- 79-1990 **The Dietary Administration of L-Monosodium Glutamate, DL-Monosodium Glutamate and L-Glutamic Acid to Rats.** (Eng) Ebert, A. G. (International Glutamate Technical Committee, P.O. Box 744, Westwood, MA, 02090). *Toxicol Lett* 3(2): 71-78; 1979.

The effects of dietary L-monosodium glutamate, DL-monosodium glutamate, and L-glutamic acid (0.1% or 0.4% of the diet for up to 2 yr beginning at 12 wk of age) were studied in Sprague-Dawley rats. None of the treatments affected body wt gain, food intake, general behavior, hematologic parameters, organ wt, or fertility. Combined survival to 730 days was 57.3% for the treated rats and 59.3% for controls. Tumor incidence was 40.1% in the treated animals and 42.4% in the controls. Most tumors in females were mammary adenomas and most in males were benign tumors of dermal origin. The findings are essentially in agreement with others published in the literature. (11 refs)

- 79-1991 **The Dietary Administration of Monosodium Glutamate or Glutamic Acid to C-57 Black Mice for Two Years.** (Eng) Ebert, A. G. (International Glutamate Technical Committee, P.O. Box 744, Westwood, MA, 02090). *Toxicol Lett* 3(2): 65-70; 1979.

The effects of dietary L-monosodium glutamate, DL-monosodium glutamate (DL-MSG), and L-glutamic acid (1.0% or 4.0% of the diet for 715 days) on tumorigenesis were studied in male C57 black mice. There was no consistent relationship between treatment and mortality. Hematologic findings at 280 days did not differ between control and treated mice. Histopathologic examination of gross lesions detected at postmortem and of routine visceral tissue samples revealed only a single neoplasm--a benign lung adenoma in a mouse given 1% DL-MSG. The other histologic changes were indicative of age or chronic inflammatory processes and did not differ between control and treated mice groups. Thus, no evidence of carcinogenic potential was found for any of the substances tested. (5 refs)

- 79-1992 **Promoting Effect of Saccharin and DL-Tryptophan in Urinary Bladder Carcinogenesis.** (Eng) Cohen, S. M. (Dept. Pathology, St. Vincent Hosp., Worcester, MA, 01504); Arai, M.; Jacobs, J. B.; Friedell, G. H. *Cancer Res* 39(4): 1207-1217; 1979.

The existence of at least two stages in bladder carcinogenesis was investigated in male Fischer rats using N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT: 0.2% of diet for 6 wk; av cumulative dose 1.5 g) as the initiator. Sodium saccharin (SS) and DL-tryptophan (TP) were fed at 5% and 0.2% of the diet, respectively, starting either immediately after or 6 wk after FANFT administration. After 2 yr, rats fed the control diet (42 rats), SS (20), or TP (20) had no urinary bladder lesions. The group fed FANFT followed by control diet developed one papilloma and four bladder carcinomas. All rats fed FANFT for 36 wk or for their lifetime (78 rats) had bladder carcinomas, and several had invasive lesions. Rats fed FANFT + SS or TP, either immediately after FANFT feeding or after FANFT + 6 wk of control diet, developed high incidences of bladder cancer. SS was a much more potent promoting agent than TP, inducing higher incidences of bladder tumors with a shorter latent period and producing tumors that were more invasive. Sequential epithelial changes were observed by scanning and transmission electron microscopy as well as by light microscopy. Pleomorphic microvilli were present on the superficial cells of all tumors examined and on the surface cells of hyperplastic bladder epithelium after 6 wk of FANFT + 6 wk of SS, but not after 6 wk of FANFT + 6 wk of control diet or 6 wk of TP. These results are consistent with the two stage theory of urinary bladder carcinogenesis and suggest that SS and TP might act as tumor-promoting agents. (68 refs)

79-1993 Microbial Co-culture Systems Involved in Colon Cancer? Synchronized Production of Both Promoter and Initiator (Meeting Abstract). (Eng) Yokoyama, M. T. (Michigan State Univ., East Lansing, MI, 48824); Beeman, S. C. *Fed Proc* 38(3, part 1): 864; 1979. (no refs)

79-1994 Absence of Carcinogen-induced Unscheduled DNA Synthesis in NAD-depleted 3T3 Cells (Meeting Abstract). (Eng) Jacobson, E. L. (Texas Women's Univ., Denton, TX, 76204); Narasimhan, G. *Fed Proc* 38(3, part 1): 619; 1979. (no refs)

79-1995 Chemical Carcinogens Produce Mutations to Ouabain Resistance in Transformable C3H/10T1/2 Cl 8 Mouse Fibroblasts. (Eng) Landolph, J. R. (Los Angeles County-Univ. Southern California Comprehensive Cancer Center., Los Angeles, CA, 90033); Heidelberger, C. *Proc Natl Acad Sci USA* 76(2): 930-934; 1979.

A mutation assay for ouabain-resistant mutants in the transformable C3H/10T1/2 Cl 8 mouse fibroblast cell line, in which there is a correspondence between morphologic and malignant transformation, is described. Chemical carcinogens induce mutations to ouabain resistance in C3H/10T1/2 Cl 8 cells. The mutant phenotype is stable and heritable in the absence of a selective agent, and dose-response curves for mutation frequency were obtained with N-methyl-N'-nitro-N-nitrosoguanidine, 3-methylcholanthrene, benzo(a)pyrene (BP), N-acetoxy-N-2-acetylaminofluorene and anti-7,8-diol-9,10-epoxide of BP. The ratio of the malignant transformation frequency to the mutation frequency was 12 for BP and 21 for N-acetoxy-N-2-acetylaminofluorene. With this mutation assay the C3H/10T1/2 Cl 8 cell line can be used to compare mutation and transformation frequencies to screen for xenobiotics that pose mutagenic or carcinogenic hazards to mammalian cells. (35 refs)

79-1996 Fatty Acids, Oral Contraceptive and Aflatoxin Interrelationships (Meeting Abstract). (Eng) Rogel, A. (Sch. Public Health, Univ. California Los Angeles, Los Angeles, CA, 90024); Aftergood, L.; Alfin-Slater, R. B. *Fed Proc* 38(3, part 1): 713; 1979. (no refs)

79-1997 Mutagenicities of 4-Hydroxy-1,4-benzoxazinones Naturally Occurring in Maize Plants and of Related Compounds. (Eng) Hashimoto, Y. (Faculty Pharmaceutical Science, Univ. Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan); Shudo, K.; Okamoto, T.; Nagao, M.; Takahashi, Y.; Sugimura, T. *Mutat Res* 66(2): 191-194; 1979.

The mutagenicity of two naturally occurring 4-hydroxyben-

zoxazinones and eight synthetic analogs was assayed in the *Salmonella typhimurium*/rat liver microsome system. 2,4-Dihydroxy-1,4-benzoxazinone and 2,4-dihydroxy-7-methoxy-1,4-benzoxazinone, which occur naturally in such cereal plants as maize, wheat, and rye, and 4-hydroxy-7-methoxybenzoxazinone and 4-hydroxy-6-methoxybenzoxazinone were mutagenic in *Salmonella* strains TA100 and TA98. The presence of the 2-hydroxy group or the 7-methoxy group seems to be required for mutagenic activity. The two naturally occurring compounds have sufficiently high specific mutagenicities to be regarded as naturally occurring mutagens and further studies are required on their distribution in plants and animal foods. (11 refs)

79-1998 Effects of Some Carcinogens on Conformation of Histones. (Eng) Su, Y. Y. (Neurosensory Center, Baylor Coll. Medicine, Houston, TX, 77030); Jirgensons, B. *Makromol Chem* 180(2): 367-373; 1979.

The effects of 4-nitroquinoline N-oxide (4-NQO), 13-H-dibenzo(c,j)carbazole (13-HDBC), and 7-H-dibenzo(c,g)carbazole (7-HDBC) on the conformation of histones F1 (H1), F2a (H2A), F2b (H2B), and F3 (H3) were studied using a circular dichroism (CD) probe. 4-NQO had no effect on the tertiary structure of F1, whereas the two carbazoles modified it slightly. The main chain conformation of F1 was not affected by any of the carcinogens. The tertiary structure of F2a was affected by all three carcinogens, with the strongest enhancement of the CD bands assigned to tyrosine and phenylalanine chromophores being produced by 7-HDBC. 4-NQO had a very weak effect on the main chain conformation of F2a, but the two carbazoles promoted helix formation of this histone. The effects of the carcinogens on F2b were similar to those on F2a but not as pronounced. 7-HDBC produced extrinsic Cotton effects in the 300- to 380-nanometer (nm) spectral zone of F2a and F2b. The main chain conformation of F3 was not significantly affected by the carcinogens. However, both carbazoles enhanced the bands related to the tyrosine and phenylalanine chromophores and produced extrinsic Cotton effects in the 300- to 380-nm spectral zone. The results show that the three carcinogens interacted with some of the histone fractions, thereby altering the conformation of the histones. (20 refs)

79-1999 Further Characterization of Atypical Acinar Cell Nodules (AACN) of the Pancreas in Carcinogen Treated Rats (Meeting Abstract). (Eng) Shinozuka, H. (Dept. Pathology, Univ. Pittsburgh, Pittsburgh, PA, 15261); Katyal, S. L. *Fed Proc* 38(3, part 2): 1403; 1979. (no refs)

79-2000 Histochemical Differences Between So-Called

79-2000 Megalocytosis and Neoplastic or Preneoplastic Liver Lesions Induced by N-Nitrosomorpholine. (Eng) Taper, H. S. (Dept. General Pathology and Neuropathology, Univ. Louvain, avenue E. Mounier, 52 (ANPG 52.60), B-1200 Bruxelles, Belgium); Bannasch, P. *Eur J Cancer* 15(2): 189-196; 1979.

The histochemistry of the so-called megalocytes and preneoplastic or neoplastic hepatocytes was studied in the livers of male Sprague-Dawley rats treated with N-nitrosomorpholine (NNM: max of 20 ml/day of a 50% aqueous soln as drinking water for 3 wk). Immediately after NNM treatment, the lobular architecture of the liver parenchyma was greatly altered by hepatocellular necrosis, a pronounced loss of the parenchyma, and an intense reactive proliferation of bile ducts or mesenchymal cells. The megalocytes, which are very numerous, had a cytoplasm poor in glycogen and rich in pyroninophilic material. Nuclease activity was normal or increased. The clear and acidophilic hepatocytes, which are considered to be preneoplastic, showed excessive storage of glycogen and usually had decreased or absent nuclease activity. Most of the megalocytes disappeared within 3 wk after withdrawal of the carcinogen, whereas the clear and acidophilic cells persisted for up to 50 wk. The latter cells were found in the numerous foci and rare neoplastic nodules containing altered liver cells. Fifty weeks after withdrawal of NNM, three of four rats had hepatocellular carcinomas. The cells of these tumors showed distinct basophilia, a complete absence of glycogen, and an almost complete absence of nuclease activity. The megalocytes appeared to result from an interaction between toxic and regenerative events. (19 refs)

79-2001 Conversion of 2,4,6-Trinitrophenol to a Mutagen by *Pseudomonas aeruginosa*. (Eng) Wyman, J. F. (Naval Biosciences Lab., Sch. Public Health, Univ. California, Berkeley, CA, 94720); Guard, H. E.; Won, W. D.; Quay, J. H. *Appl Environ Microbiol* 37(2): 222-226; 1979.

The biodegradation of 2,4,6-trinitrophenol (picric acid) by *Pseudomonas aeruginosa* and its mutagenicity for *Salmonella typhimurium* were studied. Anaerobic incubation of *P. aeruginosa* with picric acid resulted in a 2-log increase in cell number during the first 24 hr, followed by a relative stability in bacterial counts (10^5 - 10^7 cells/ml) for 30 days. Reduction of picric acid to 2-amino-4,6-dinitrophenol (picramic acid) by the bacteria was shown by a change in the color of the medium from yellow to reddish brown. Thin-layer chromatography, nuclear magnetic resonance, and UV spectrometry identified two of the three substances present as picric and picramic acids; the third degradation product was not identified. The picric acid concentration in the medium decreased approx 22% during the 30 days of incubation, with approx 1.7% of the concentration that was lost being converted to picramic acid. Picric acid (10 µg/plate) was mutagenic to *S. typhimurium* (frameshift and base-substitution mutations) only after activation with a rat liver homogenate preparation. Picramic acid proved to be a potent base-substitution muta-

gen and a somewhat weaker frameshift mutagen without activation by the rat liver preparation. (16 refs)

79-2002 Evidence for Covalent Binding of ^3H -Benzene to Mouse Liver Protein (Meeting Abstract). (Eng) Longacre, S. L. (Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA, 19107); Kocsis, J. J.; Snyder, R. *Fed Proc* 38(3, part 1): 683; 1979. (1 ref)

79-2003 Carcinogenicity and Chronic Toxicity of 2,4-Toluenediamine in F344 Rats. (Eng) Cardy, R. H. (Dept. Pathology, Litton Bionetics, 5516 Nicholson Lane, Kensington, MD, 20795). *J Natl Cancer Inst* 62(4): 1107-1116; 1979.

The aromatic amine 2,4-toluenediamine, which is used in the manufacture of polyurethane foams, was fed at levels of 50 and 100 ppm to inbred, barrier-raised F344 rats for 2 yr. The high dose induced a statistically significant increase in the incidence of hepatic neoplasia in males, and it induced a significant dose-related positive trend in the incidence of liver neoplasms in both sexes. Hepatocellular changes (foci and larger areas of clear cell-type cellular alteration and a few basophilic foci) considered to be associated with neoplasia were increased at a high level of statistical significance in both sexes. In addition, the compound caused statistically significant increases in the incidence of mammary tumors in females and an increase of mammary tumors in males that, although not significant statistically, was nevertheless considered to be related to the chemical. The compound was hepatotoxic and it accelerated the development of chronic renal disease in this strain, an effect that contributed to a marked decrease in the survival of dosed animals. (8 refs)

79-2004 The Decreased Degradation of Various Cell Constituents During Azodye-induced Carcinogenesis (Meeting Abstract). (Eng) Fiala, S. (Veterans Admin. Medical Center, Martinsburg, WV, 25401); Kettering, W. G. *Fed Proc* 38(3, part 2): 1403; 1979. (1 ref)

79-2005 Analgesic Nephropathy and Urinary-Tract Carcinoma. (Eng) Gonwa, T. A. (Bowman Gray Sch. Medicine, Wake Forest Univ., Winston-Salem, NC); Buckalew, V. M.; Corbett, W. T. *Ann Intern Med* 90(3): 432-433; 1979.

Epidemiologic studies implicating analgesic abuse in the development of urinary tract carcinomas are reviewed, and a case report illustrating the typical features of urinary tract cancer in analgesic abusers is presented. Approx 130 cases of urinary tract carcinomas related to analgesic abuse have

been reported worldwide. In all cases, phenacetin (PA) was the suspected carcinogen. When rats were fed PA for up to 110 wk, they developed a high degree of urothelial hyperplasia with some dysplasia. Metabolites of PA that were isolated from rats fed PA were carcinogenic in rats. The case report is that of a 37-yr-old woman with a history of sterile pyuria and chronic headache. Bilateral renal papillary necrosis was discovered following the onset of hematuria. A transitional cell carcinoma of the bladder and ureter was removed 2 yr later, but the patient died of metastatic disease 1 yr following surgery. She had consumed four to six headache powders (each containing 325 mg PA) daily for at least 20 yr before her death. (10 refs)

- 79-2006 Tumors on Sprague-Dawley Rats Induced by Long-Term Feeding of Phenacetin.** (Eng) Isaka, H. (Dept. Pathology, Kagoshima Univ. Sch. Medicine, 1208-1 Usuki-cho, Kagoshima 890, Japan); Yoshii, H.; Otsuji, A.; Koike, K.; Nagai, Y.; Koura, M.; Sugiyasu, K.; Kanabayashi, T. *Gann* 70(1): 29-36; 1979.

The carcinogenicity of phenacetin (PA) was studied in male and female Sprague-Dawley rats, who were fed a 2.5% or 1.25% PA diet for 18 mo and then a basal diet for 6 mo. The mortality rats in the PA-treated animals was 65%, compared with 20%-40% in control rats fed only the basal diet. Tumors developed in 26/27 males and 21/27 females given 2.5% PA, 20/22 males and 19/25 females given 1.25% PA, and 1/19 males and 6/25 females in the control group. Tumors first appeared in the 2.5% PA group at 47 wk and in the 1.25% PA group at 60 wk. The target organs of PA carcinogenesis were the nasal cavity (adenocarcinoma, squamous cell carcinoma, and transitional cell carcinoma) and urinary tract (renal cell carcinoma, transitional cell carcinoma). In the control group, tumors appeared in the lung, mammary gland, uterus, large intestine, and pituitary gland. The control tumors were regarded as strain-specific spontaneous tumors of Sprague-Dawley rats; they occurred more frequently in the PA-treated rats than in the controls. The results indicate that PA is carcinogenic in rats. (19 refs)

- 79-2007 Separation and Characterization of Highly Purified Forms of Liver Microsomal Cytochrome P-450 from Rats Treated with Polychlorinated Biphenyls, Phenobarbital, and 3-Methylcholanthrene.** (Eng) Ryan, D. E. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NJ, 07110); Thomas, P. E.; Korzeniowski, D.; Levin, W. *J Biol Chem* 254(4): 1365-1374; 1979.

The chromatographic separation of three highly purified forms of cytochrome (CC) P-450 (P-450a, P-450b, and P-450c), isolated from the hepatic microsomes of rats treated with the polychlorinated biphenyl mixture Aroclor 1254 is described. Each form showed a single protein-staining band

on sodium dodecyl sulfate-polyacrylamide gels with a minimum mol wt of 48,000 (P-450a), 52,000 (P-450b), and 56,000 (P-450c). CC's P-450a and P-450b were obtained from phenobarbital (PB)-treated rats, and CC's P-450a and P-450c were isolated from 3-methylcholanthrene (3-MC)-treated rats. CC P-450b was the major hemeprotein inducible by PB, and CC P-450c was the predominant hemeprotein induced by 3-MC. The CO-reduced difference spectral peak of CC P-450a was at 452 nanometers (nm), that of P-450b at 450 nm, and that of P-450c was at 447 nm. CC P-450a preferentially hydroxylated testosterone at the 7 α position but has low catalytic activity for the metabolism of benzphetamine, benzo(a)pyrene, 7-ethoxycoumarin, and zoxazolamine. CC P-450b catalyzes the hydroxylation of testosterone at the 16 β position and the demethylation of benzphetamine most efficiently. CC P-450c had very high catalytic activity for benzo(a)pyrene and zoxazolamine hydroxylation and 7-ethoxycoumarin O-dealkylation. Aniline was hydroxylated by the three forms of CC P-450 at comparable rates. Antisera prepared against CC's P-450a, P-450b, or P-450c did not cross-react with the heterologous antigens in Ouchterlony double-diffusion plates. When CC's P-450a, P-450b, and P-450c were subjected to limited proteolysis in the presence of sodium dodecyl sulfate, the resulting peptide maps provided additional evidence that these hemeproteins are structurally distinct. The forms of CC P-450 obtained from PB- and 3-MC-treated rats were indistinguishable from the corresponding forms from Aroclor 1254-treated rats by all criteria examined. (61 refs)

- 79-2008 Induction of Hepatic Mixed Function Oxidases in Senescent Rodents-II. Effect of Polychlorinated Biphenyls.** (Eng) Birnbaum, L. S. (Masonic Medical Lab., Utica, NY, 13503); Baird, M. B. *Exp Gerontol* 13(6): 469-477; 1978.

The effect of polychlorinated biphenyls (PCB's: 500 mg/kg Aroclor 1254 ip 5 days before sacrifice) on the age-related decline in coordinated hepatic monooxygenase activities was studied in male CFN rats. Hepatic microsomal levels of cytochrome P-450, NADPH cytochrome c reductase, and total lipid (mg lipid/mg microsomal protein) and the ability to respond to an inductive challenge of PCB's did not change significantly with age. Levels of NADPH cytochrome P-450 reductase, phospholipid [(PL): μ g PL phosphate/mg microsomal protein], and PL lipid (μ g PL phosphate/mg lipid) decreased with age, but the decreases were all at least partially reversed by treatment with PCB. The age-related difference in the metabolism of ethylmorphine and benzphetamine was also obliterated by PCB, and benzo(a)pyrene hydroxylase activity was affected by PCB to a greater extent in old rats than in young rats. Multiple cytochrome P-450 peptides were present in the region between 45,000 and 60,000 daltons on polyacrylamide gel slabs, but of four peptides present in both untreated and PCB-treated rats, only the 52,000-dalton species may represent a cytochrome P-450 molecule common to both. Electrophoretic profiles were the same for young,

middle-aged, and old rats. The results indicate that old rats exhibit no age-related impairment in their capacity to respond to inducers of hepatic drug metabolism. (47 refs)

- 79-2009 Reduction of 4-(5-Nitro-2-furyl)thiazole by Rat Liver Subcellular Fractions (Meeting Abstract).** (Eng) Swaminathan, S. (Dept. Human Oncology, Univ. Wisconsin Center for Health Sciences, Madison, WI, 53792); Lower, G. M.; Bryan, G. T. *Fed Proc* 38(3, part 1): 369; 1979. (no refs)

- 79-2010 Mutagenicity of the Non-carcinogenic Dibenzylnitrosamine and an Alpha-Acetoxy Derivative.** (Eng) Jacobson, M. K. (Dept. Chemistry, North Texas State Univ. at Denton, Denton, TX, 76203); Barton, R. A.; Yoder, S. S.; Sigh, S.; Lyle, R. E. *Cancer Lett* 6(2): 83-87; 1979.

The mutagenicity of a noncarcinogenic nitrosamine, N,N-dibenzylnitrosamine, and a chemically synthesized α -acetoxy derivative, N-(α -acetoxybenzyl)-N-benzylnitrosamine, was assayed in *Salmonella typhimurium* TA100 and TA1535. N,N-dibenzylnitrosamine was not mutagenic at doses up to 2 micromoles when tested directly or in the presence of a metabolic activation system; higher doses were toxic to the tester strains. The α -acetoxy derivative, however, was mutagenic both with and without metabolic activation. In contrast to previous reports with another α -acetoxy nitrosamine derivative, the mutagenic response was greatly reduced in the presence of the activating system. The differences in mutagenicity between the two compounds may be due to stereochemical and/or conformational differences that affect hydrolysis rates of the acetoxy group. (13 refs)

- 79-2011 Lidocaine Uptake and DL-Propranolol Effect on Isolated Hepatocytes (Meeting Abstract).** (Eng) Chen, C. P. (Sch. Pharmacy, Univ. Connecticut, Storrs, CT, 06268); Vu, V. T.; Cohen, S. D. *Fed Proc* 38(3, part 1): 700; 1979. (no refs)

- 79-2012 Drug Metabolizing Enzymes During Feeding of the Carcinogen 2-Aminoanthraquinone (Meeting Abstract).** (Eng) Ramanathan, R. (NIH, Bethesda, MD, 20014); Reddy, T. V.; Weisburger, E. K. *Fed Proc* 38(3, part 1): 661; 1979. (no refs)

- 79-2013 Clofibrate and Malignancy (Letter to Editor).** (Eng) MacGregor, G. A. (St. Luke's Hosp., Guildford, Surrey GU1 3NT, England). *Lancet* 1(8113): 445; 1979.

The case of a 50-yr-old man who died from jejunal adenocarcinoma following 15 yr of treatment with clofibrate is presented. The patient had also taken cholestyramine intermittently for 8 yr. (5 refs)

- 79-2014 Absence of Noxious Effects of Selected Neuroleptics in Dominant-Lethal Mutagenesis Assay.** (Eng) Sykora, I. (Res. Inst. Pharmacy and Biochemistry in Prague, Branch Inst., Pardubice-Rosice, Czechoslovakia); Gandalovicova, D.; Rezabek, K. *Mutat Res* 66(3): 291-299; 1979.

No dominant-lethal effect was induced in mice by the neuroleptics prothiaden, imipramine, oxyprothepin decanoate, or docloxythepin, even when administered at doses several times greater than the clinical doses. (15 refs)

- 79-2015 Polycyclic Compounds. XII. Vicinal cis/trans-Isomeric Dihydrodiols in the Hexahydrophenanthrene and Hexahydrobenz(a)anthracene Series.** (Ger) Malchow, A. (Institut für Organische Chemie, Technischen Hochschule Darmstadt, Olshausenstrasse 40-60, D-2300 Kiel, W. Germany); Kirrstetter, R. G.; Tochtermann, W. *Chem Ber* 112(2): 532-540; 1979.

The syntheses of the vicinal trans-dihydrodiols trans-9,10-dihydroxy-9-methyl-3,4,9,10-tetrahydrophenanthrene-1(2H)-one and trans-5,6-dihydroxy-6-methyl-2,3,5,6-tetrahydrobenz[a]anthracene-4(1H)-one and their cis-isomers are described. The chemistry and biochemistry of compounds of this type are of interest because of their potential carcinogenicity and mutagenicity. (18 refs)

- 79-2016 Inhibition of the Development of the Mammary Glands of Mice with a Bromotriphenylethylene.** (Eng) Rendon, A. M. (Equipe de Recherches 190 du CNRS, Fondation Curie, 26, rue d'Ulm, 75005 Paris, France); Rudali, G.; Guggiari, M. *Biomedicine [Express]* 29(8): 276-279; 1978.

The effect of 1-bromo-2-(p-ethylphenyl)-1,2-diphenylethylene (2, 20, or 200 mg/kg diet) on mammary gland development was studied in 25-day-old female C3H/f(XVII/G) mice with isologous pituitary gland implants under the kidney capsule. This graft is associated with high prolactin levels and a high incidence of mammary cancers. Fifty days after implantation, hyperplastic alveolar nodules (HAN's) were noted in the mammary glands of untreated controls. Mammary gland development was markedly inhibited in mice treated with the two higher doses of bromotriphenylethylene, and no HAN's were present. Mammary gland development in mice treated with the lowest dose was similar to that in the con-

trols. The higher doses also prevented development of the ovaries and uterine horns. (12 refs)

- 79-2017 Morphological Study of Rotenone-induced Breast Tumors in Wistar Rats.** (Eng) Merchan, J. (Depastamento de Histologia y Anatomia Patologica, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain); Diaz-Gil, J.; Figueras, M. A.; Navarro, M. A.; Viladiu, P.; Gosalvez, M. *Rev Esp Oncol* 25(1): 107-120; 1978.

The histological features of 20 primary and 10 transplanted mammary tumors induced in Wistar rats by rotenone (0.1 to 0.2 mg/day, 5 days/wk, for 2-3 mo) were studied. Grossly, the tumors appeared as sc masses isolated from neighboring tissues by a white, fasciculated capsule. Obesity caused by extraordinary augmentation of the perivisceral adipose tissue was noted in non-tumor-bearing rats, but not in tumor-bearing rats. Light microscopy showed three patterns of tumor growth: a mixture of epithelial and connective tissue proliferation without microscopic features of malignancy; a pattern dominated by dilated ducts filled with an amorphous eosinophilic material; and a pattern of more uniform ducts with typical secretion images upon electron microscopy. The secreting acini were similar to those observed during lactation. Greatly altered cells often had normal mitochondria, whereas at times normal cells exhibited mitochondria with highly abnormal ultrastructures. The tumors showed a moderate estrogen dependence. These tumors thus resembled those of mammary fibroadenoma and fibrocystic disease in women and might be useful for studying these lesions. (24 refs)

- 79-2018 Tumors in Mice Receiving Subcutaneous Injections of δ 9 Tetrahydrocannabinol (Meeting Abstract).** (Eng) Szepeswol, J. (Dept. Biological Sciences, Florida International Univ., Miami, FL, 33199); Fletcher, J.; Toro-Goyco, E. *Fed Proc* 38(3, part 2): 1450; 1979. (no refs)

- 79-2019 Ellipticine and Derivatives Induce Breakage of L1210 Cells DNA In Vitro.** (Eng) Paoletti, C. (205 route de Narbonne, 31078 Toulouse Cedex, France); Lesca, C.; Cros, S.; Malvy, C.; Auclair, C. *Biochem Pharmacol* 28(3): 345-350; 1979.

The effect of ellipticine (E), 9-hydroxyellipticine (OHE), 2-methyl-9-hydroxyellipticinium (CH₃OHE), and 9-aminoellipticine (NH₂E) on the DNA of L1210 cells were studied. E and several of its derivatives have been reported to be cytotoxic and antitumor agents. They also bind strongly to DNA, and most of them intercalate into DNA base pairs. None of the treated L1210 cells stained with Trypan Blue, and none of the four drugs modified the oxygen consumption of the cells. However, part of the DNA extracted from treated cells

migrated less rapidly into an alkaline sucrose gradient than the bulk of the material extracted from untreated cells, which indicates that DNA fragmentation had occurred. This effect was noted within < 1 hr of drug exposure, and if the duration of exposure was increased, the fraction of slowly moving DNA was not enhanced significantly. The minimal effective DNA-breaking dose was 1,000, 20, 100, and 500 nanograms (ng)/ml for E, OHE, CH₃OHE, and NH₂E, respectively, but the doses that inhibited the rate of in vitro cell growth by 50% were 242, 3.9, 13.8, and 53 ng/ml, respectively. Removal of DNA breaks was very rapid after exposure was discontinued. One interesting observation was the limited extent of DNA degradation (< 30% of total DNA) that occurred in the treatment cells irrespective of dose or duration of exposure. (26 refs)

- 79-2020 Lysergic Acid Diethylamide and Acute Leukemia.** (Eng) Goh, K. (435 E. Henrietta Road, Rochester, NY, 14620); Bauman, A. W. *J Am Med Wom Assoc* 33(10): 419-422; 1978.

Chromosomal breakages presumably caused by lysergic acid diethylamide (LSD) have led to the speculation that there may be an increase in the incidence of leukemia among LSD users. A 23-yr-old Caucasian man with a history of taking LSD over a period of 8 mo was diagnosed with acute myeloblastic leukemia 1.5 yr later. This is the fourth reported case of acute leukemia in a patient with a history of LSD ingestion. This low incidence may reflect underreporting of LSD usage in leukemia, a lack of direct questioning of LSD usage in leukemic patients, or lack of a cause-and-effect relationship between LSD and leukemia. (9 refs)

- 79-2021 Evidence for a Mutagenic Effect of the Narcotic Antagonist, Naltrexone, in Germ Cells of *Drosophila*.** (Eng) Zimmering, S. (Div. Biology and Medicine, Brown Univ., Providence, RI, 02912). *Mutat Res* 66(2): 129-131; 1979.

The frequency of sex-linked recessive lethals produced by the narcotic antagonist N-cyclopropylmethylnoroxymorphone (Naltrexone) in *Drosophila melanogaster* at a nontoxic dose of 10 mg/ml was 0.43%. This was significantly higher than the frequency in controls (0.16%, $p < 0.001$). Results of large-scale experiments testing for chromosome breakage and nondisjunction were negative. (5 refs)

- 79-2022 Determination of Halogenated Organic Compounds and Mutagenicity Testing of Spent Bleach Liquors.** (Eng) Bjorseth, A. (Central Inst. Industrial Res., P.O. Box 350, Oslo 3, Norway); Carlberg, G. E.; Moller, M. *Sci Total Environ* 11(2): 197-211; 1979.

The organohalogenated compounds in and mutagenicities of the spent bleach liquors used in the production of paper pulp were studied. Several organohalogenated compounds that have not been reported previously were identified in these liquors. These compounds included halogenated derivatives of dimethylpropyl naphthalenes and alkylated catechols. However, approx 70% of the total organochlorine compounds were not identified. The concentrated and unconcentrated effluents were tested for mutagenicity by the Ames Salmonella test. Weak but significant mutagenicity, especially for strain TA100, was shown by the effluent from the first chlorination stage in the sulfite process, effluents from both chlorination stages in the sulfate process, and the effluent from the hypochlorite stage in the sulfate process. All concentrated extracts, except the one from the alkali stage in the sulfite process, were mutagenic. Similar results were obtained with the cyclohexane extracts of the effluents. Dichloro-p-cymene and bromo-p-cymene were weakly mutagenic without metabolic activation. Addition of liver microsomes for metabolic activation reduced the mutagenicity of all substances tested except for the effluent from the first chlorination stage in the sulfate process. (21 refs)

79-2023 The Influence of Dietary Protein Level and 7,8-Benzoflavone on the In Vivo Covalent Binding of Benzo(a)pyrene to Liver and Lung DNA (Meeting Abstract). (Eng) Falahee, K. J. (Cornell Univ., Ithaca, NY, 14853); Campbell, T. C. *Fed Proc* 38(3, part 1): 369; 1979. (no refs)

79-2024 Synthesis of 12-Fluoro-7-methylbenz(a)anthracene and 7-Fluoro-12-methylbenz(a)anthracene. (Eng) Newman, M. S. (Dept. Chemistry, Ohio State Univ., Columbus, OH, 43210); Khanna, J. M. *J Org Chem* 44(5): 866-868; 1979.

The synthesis of 12-fluoro-7-methylbenz(a)anthracene (12-F-7-MBA) and 7-fluoro-12-methylbenz(a)anthracene (7-F-12-MBA), compounds related to 7,12-dimethylbenz(a)anthracene (DMBA), the most carcinogenic dimethylbenz(a)anthracene hydrocarbon known, is described. These compounds were synthesized in order to provide more information as to why the methyl (Me) group at position 12 in DMBA should increase the activity of 7-methylbenz(a)anthracene. It is possible that the Me at 12 is metabolized to give a more potent carcinogen, that it blocks a detoxification mechanism that occurs at 12, or the steric effect of the 12-Me group causes sufficient intramolecular overcrowding that the noncoplanar DMBA is more easily metabolized to the ultimate carcinogen. 12-F-7-MBA is the last of the monofluoro-7-MBA's to be tested. Furthermore, the testing of 12-F-7-MBA is considered particularly important because the 12-fluoro group should not only prevent any metabolism at 12, but the steric effect of the F at 12 is considerably less than that of a Me group. 7-F-12-MBA was synthesized to

determine if it is as carcinogenic as DMBA, a finding that would cast light on the mechanism by which DMBA produces cancer, because an F at position 7 would block a detoxification pathway and would make impossible a carcinogenic mechanism that involves metabolism at the 7-Me group of DMBA. (17 refs)

79-2025 In Vitro N-Hydroxylation of 4-Aminobiphenyl (Meeting Abstract). (Eng) Turner, J. C. (Lilly Res. Lab., Indianapolis, IN, 46206); Whitaker, G.; McMahon, R. E. *Fed Proc* 38(3, part 1): 683; 1979. (no refs)

79-2026 Chromosomal Aberration Tests on 29 Chemicals Combined with S9 Mix In Vitro. (Eng) Mat-suoka, A. (Div. Mutagenesis, Biological Safety Res. Center, Natl. Inst. Hygienic Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158, Japan); Hayashi, M.; Ishidate, M. *Mutat Res* 66(3): 277-290; 1979.

A metabolic activation system consisting of a rat liver microsome fraction plus cofactors (S9 mix) was incorporated in an in vitro chromosome aberration test for screening environmental chemical mutagens/carcinogens. Chinese hamster lung (CHL) cells were incubated with 1 of the 29 chemicals evaluated in the presence or absence of S9 mix. The test chemicals included 4 dialkylnitrosamines, 9 additional compounds known to be procarcinogens, 8 pharmaceutical drugs, 2 pesticides, 3 food additives, and 3 industrial chemicals. The dialkylnitrosamines only induced chromosome aberrations when they were treated with S9 mix. The incidence of chromosome aberrations varied with incubation time, recovery time, components of the S9 mix, and the agent used to induce the microsomal enzymes (polychlorinated biphenyl, phenobarbital, or 3-methylcholanthrene). For dimethylnitrosamine, max incidence was obtained when the cells were incubated with S9 mix for 3 hr and harvested 24 hr after treatment. Therefore, this procedure was routinely applied to the remaining chemicals. Ten of 16 known carcinogens induced aberrations when they were treated with S9 mix. The remaining six carcinogens induced few or no aberrations even after activation. The two insecticides, allethrin and diazinon, were strongly positive at relatively low doses only when they were activated with the S9 mix. Three drugs, ethenzamide, methyl p-hydroxybenzoate, and nitrofurazone, and the food additive sodium hypochlorite were positive on activation. The two industrial chemicals, styrene monomer and tris-dichloropropylphosphate, were also positive in this activation system. This assay is concluded to be useful for screening environmental mutagens/carcinogens. Chemicals that were positive in the assay should be regarded as being suspicious and should be tested further in animals. (25 refs)

79-2027 Comparison of Metabolism-mediated Binding to DNA of 7-Hydroxymethyl-12-methylbenz(a)anthracene and 7,12-Dimethylbenz(a)anthracene. (Eng) Dipple, A. (Molecular Aspects Chemical Carcinogenesis, Frederick Cancer Res. Center, P.O. Box B, Frederick, MD, 21501); Tomaszewski, J. E.; Moschel, R. C.; Bigger, C. A.; Nebzzydowski, J. A.; Egan, M. *Cancer Res* 39(4): 1154-1158; 1979.

The binding of 7-hydroxymethyl-12-methylbenz(a)anthracene and 7,12-dimethylbenz(a)anthracene (DMBA) to DNA catalyzed by mouse embryo cells or by rat liver microsomes was studied to determine if the metabolic activation of DMBA for DNA binding involves an initial conversion to a 7-hydroxymethyl derivative. The binding of DMBA to the DNA of mouse embryo cells in culture was an order of magnitude greater than that of the hydroxy compound throughout a dose range up to 0.1 µg hydrocarbon/ml of medium. The 7-hydroxymethyl derivative and DMBA formed nucleoside adducts that exhibited different chromatographic and fluorescence spectral properties. There was no indication, in the analysis of the DMBA products, of any product that might have arisen from the further metabolism of any hydroxymethyl derivative generated by metabolism. It is concluded that the hydroxy compound is not an intermediate in the binding of DMBA to DNA in these systems. The binding of the hydroxymethyl derivative to DNA was inhibited by 1,1,1-trichloropropylene 2,3-oxide, an inhibitor of epoxide hydrazase. This result and the fluorescence spectra of the hydroxy compound-DNA adducts indicate that the hydroxy compound is activated for DNA binding through the formation of a diol-epoxide in the 1,2,3,4-ring. As previously demonstrated for DMBA, this is consistent with the activation of the hydroxy compound through a bay-region diol-epoxide. (26 refs)

79-2028 Distribution of 7,12-Dimethylbenz(a)anthracene (DMBA) in Serum Proteins, In Vivo (Meeting Abstract). (Eng) Penn, A. (New York Univ., Inst. Environmental Medicine, New York, NY, 10016); Dreessen, M.; Batastini, G. *Fed Proc* 38(3, part 2): 1063; 1979. (no refs)

79-2029 Mutagenic Effect of 7,12-Dimethylbenz(a)anthracene-epidioxide on *Salmonella typhimurium*. (Eng) Tu, M. H. (Northwestern Univ. Dental Sch., Chicago, IL, 60611); Perry, D.; Chen, C. *Mol Pharmacol* 15(1): 189-191; 1979.

A modified Ames mutagenicity assay in which light was used for activation instead of liver microsomes was chosen as a preliminary screening device to determine whether 7,12-dimethylbenz(a)anthracene-7,12-epidioxide (DMBAO₂) can be an ultimate carcinogen. Incubation of *Salmonella typhimurium* TA100 with 7,12-dimethylbenz(a)anthracene (DMBA) in the absence of light resulted in an increased frequency of mutation. Light alone also caused some revertants.

Increased reversion was observed with increased light exposure and DMBA concentration until lethality exceeded mutagenesis. DMBAO₂ exposed to light for 24 hr was no more mutagenic than light alone, although 48 hr exposure to light rendered it more lethal. The data suggest that the bioactivated ultimate mutagen of DMBA could be DMBAO₂ and that light can activate a mutagen in situ to a specific reactive compound. (9 refs)

79-2030 Metabolism of Benzo[a]anthracene to Its Tumorigenic 3,4-Dihydrodiol. (Eng) Thakker, D. R. (Section Oxidation Mechanisms, Lab. Chemistry, Natl. Inst. Arthritis, NIH, Bethesda, MD, 20014); Levin, W.; Yagi, H.; Ryan, D.; Thomas, P. E.; Karle, J. M.; Lehr, R. E.; Jerina, D. M.; Conney, A. H. *Mol Pharmacol* 15(1): 138-153; 1979.

High-pressure liquid chromatography was used to analyze the products of the metabolism of benz(a)anthracene (BA) by rat liver microsomes and by a highly purified and reconstituted monooxygenase system. Metabolism of BA by purified cytochrome P-448 or liver microsomes from untreated, phenobarbital-treated, or 3-methylcholanthrene-treated rats yielded primarily BA 5,6-dihydrodiol and a mixture of BA 3,4-, 8,9-, and 10,11-dihydrodiols in the presence of epoxide hydrazase (EH); only trace amounts of phenols were formed. In the absence of EH, only phenols and the K-region 5,6-oxide were formed. In the presence of EH, max metabolism was 40%, whereas in the absence of EH, max metabolism was 9%. BA 5,6-oxide was a poor inhibitor of BA metabolism, 8- and 9-hydroxy-BA were moderate inhibitors (26% and 35% inhibition, respectively), and 5- and 6-hydroxy-BA were strong inhibitors (88%-89% inhibition). Unidentified phenols or non-K-region arene oxides derived from the parent hydrocarbon were responsible for the observed inhibition. The data indicate that the low carcinogenicity of BA may be explained at least in part by the low percentage of the highly tumorigenic BA 3,4-dihydrodiol formed among the metabolites of BA. (69 refs)

79-2031 Prophylactic Effect of BCG Cell-Wall Skeleton on the Tumor Induction by 7,12-Dimethylbenz[a]anthracene in Mice: Strain Difference. (Eng) Ikegami, R. (Dept. Oncogenesis, Osaka Univ. Medical Sch., Fukushima 1-1-50, Fukushima-ku, Osaka 553, Japan); Takatsu, K.; Ono, S.; Hamaoka, T.; Fujiwara, H.; Kitagawa, M.; Azuma, I.; Yamamura, Y. *Gann* 70(1): 101-107; 1979.

The effect of oil-attached BCG cell-wall skeletons (BCG-CWS, 100 µg given iv every 2 wk for 14 wk) on the tumorigenicity of 7,12-dimethylbenz(a)anthracene (DMBA, 500 µg given sc 7 days after the first BCG-CWS injection) was studied in various strains of mice. BCG-CWS significantly reduced DMBA carcinogenesis in male ddO mice, but it had no effect on the histologic appearance of the tumors (all

were squamous cell carcinomas). BCG-CWS injected sc into the site of DMBA injection was also effective, whereas ip administration was not. When given 3 to 7 wk after DMBA, BCG-CWS was less or noneffective in reducing tumor incidence. Tumor growth was significantly reduced in C57BL/6 and BALB/c mice by BCG-CWS treatment, but the same treatment had little effect in BTK and C3H/He mice. Thus, although BCG-CWS treatment (by an appropriate route and timing) appears to be effective in reducing DMBA carcinogenesis, the effectiveness varies in different strains of mice. (20 refs)

- 79-2032 Tumor Initiators and Promoters in the Induction of Epstein-Barr Virus.** (Eng) zur Hausen, H. (Institut für Virologie, Zentrum für Hygiene, Universität Freiburg, Hermann-Herder-Strasse 11, 7800 Freiburg, W. Germany); Bornkamm, G. W.; Schmidt, R.; Hecker, E. *Proc Natl Acad Sci USA* 76(2): 782-785; 1979.

The effect of various tumor initiators and promoters on the induction of Epstein-Barr virus (EBV) in different lymphoblastoid cell lines was analyzed. Neither five polycyclic aromatic hydrocarbons [including the potent tumor initiator 7,12-dimethylbenz(a)anthracene] nor the potent (ultimate) hepatocarcinogen N-acetoxy-N-2-acetylaminofluorene induced EBV. A series of compounds representing three classes of tumor-promoting diterpene esters (eg, 12-O-tetradecanoylphorbol-13-acetate) efficiently induced EBV in persistently infected cells. The concentration required for max induction ranged between 0.5 and 100 nanomolar. Some nonpromoting diterpenes (phorbol, 4 α -phorbol-12,13-didecanoate, and ingenol) did not induce EBV. However, the nonpromoters resiniferatoxin and 12-deoxyphorbol-13-decatrienoate were effective, whereas anthralin, a tumor promoter, was not. In three lines of EBV genome-carrying cells (Raji, NC-37, and RPMI 64-10), only abortive induction was noted, leading exclusively to the synthesis of early antigen. When lines with low spontaneous virus release (P3HR-1, B95-8, and QIMR-Wil) were treated with tetradecanoylphorbol acetate, approx 20-40 times more viral DNA was recovered compared with the amount in untreated controls. Viral DNA from tetradecanoylphorbol acetate-induced cultures had the same restriction endonuclease cleavage pattern as viral DNA obtained from noninduced cells. Within 10 days after induction, release of infectious virus increased approx by one order of magnitude. Prostaglandins, reported to be released after treatment with tumor promoters, were ineffective in inducing virus under the conditions tested. (23 refs)

- 79-2033 DMBA Induced Tumor Incidence in Rats Maintained on Wheat Gluten Diet for Generations** (Meeting Abstract). (Eng) Hsueh, A. M. (Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205); Kellum, M. J. *Fed Proc* 38(3, part 1): 713; 1979. (no refs)

- 79-2034 Identification of 7,12-Dimethylbenz(a)anthracene-2-ol from Cultured Hamster Cells: Evidence for Formation of 7,12-Dimethylbenz(a)anthracene-1,2-oxide** (Meeting Abstract). (Eng) Oravec, C. T. (Ohio State Univ., Columbus, OH, 43210); Daniel, F. B.; Wong, L. K.; Wang, C. L. *Fed Proc* 38(3, part 1): 662; 1979. (no refs)

- 79-2035 Tumor Promotion by Abrasion Induced Epidermal Hyperplasia in the Skin of Mice** (Meeting Abstract). (Eng) Argyris, T. S. (State Univ. New York, Upstate Medical Center, Syracuse, NY, 13210). *Fed Proc* 38(3, part 2): 1073; 1979. (no refs)

- 79-2036 On the Biochemical Mechanism of Tumorigenesis in Mouse Skin. IX. Interrelation Between Tumor Initiation by 7,12-Dimethylbenz(a)anthracene and the Activities of Epidermal Arylhydrocarbon Monooxygenase and Epoxide Hydratase.** (Eng) Pyerin, W. G. (Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, Germany); Hecker, E. *Z Krebsforsch* 93(1): 7-30; 1979.

The effects of 7,8-benzoflavone (BF), 2-diethylaminoethyl-2,2-diphenylvalerate HCl (SKF 525-A), and phenobarbital (PB) on tumor initiation by topical 7,12-dimethylbenz(a)anthracene (DMBA) and on arylhydrocarbon hydroxylase (AHH) and epoxide hydratase (EH) activities were studied in female NMRI mice. SKF 525-A, a selective inhibitor of cytochrome P-450, and PB, an inducer of cytochrome P-450, had no effect on DMBA tumor initiation, whereas BF, a selective inhibitor of cytochrome P-448, reduced tumor yield by up to 30% when applied with or up to 7 hr after DMBA. DMBA caused a dose-dependent increase in tumor yield and in the specific activity of epidermal AHH, but it did not affect the specific activity of EH. Topical PB had no effect on AHH activity, whereas SKF 525-A and BF reduced AHH activity up to 30% within 2-4 hr following the application of SKF 525-A or BF, but it increased to >200% of control values at 24 hr after the application of BF. None of the test compounds affected the specific activity of EH. Comparison of the time-dependence of the inhibition of tumor initiation by BF and of the DMBA-induced increase in AHH activity indicated that the effects of DMBA on tumor initiation and AHH induction were unrelated. (55 refs)

- 79-2037 Effects of 13 *cis* and all *trans* Retinoic Acid on the Development of Bladder Cancer in Rats** (Meeting Abstract). (Eng) Tannenbaum, M. (Columbia Univ., New York, NY, 10032); Tannenbaum, S.; Richelo, B. N.; Trown, P. W. *Fed Proc* 38(3, part 2): 1073; 1979. (no refs)

- 79-2038** Age as a Modifying Factor of 7,12-Dimethylbenz(a)anthracene-induced Mammary Carcinogenesis in the Lewis Rat. (Eng) Haslam, S. Z. (Lady Davis Inst. Medical Res., Jewish General Hosp., Montreal H3T 1E2, Canada). *Int J Cancer* 23(3): 374-379; 1979.

The influence of age at 7-12-dimethylbenz(a)anthracene (DMBA) administration on mammary tumorigenesis and regression was studied in female Lewis rats. Two classes of tumor were found after DMBA treatment (single intragastric dose of 15 mg/100 g): progressively growing tumors (PGT) and spontaneously regressing tumors (SRT). Both were first palpable 2-3 mo after treatment, but the SRT never exceeded a diameter of 1 cm and they regressed to a nonpalpable state. A total of 156 PGT and SRT tumors developed, 153 of them adenocarcinomas. PCT developed throughout the 12-mo experimental period, reaching a final incidence rate of 55%-84%. PGT incidence, mean latent period of PGT development, mean numbers of PGT per PGT-bearing rat, and the relative proportion of PGT that were ovary-dependent tumors (ODT: 65%-91%) were similar for all age groups at the end of 12 mo. Twenty-five percent to 39% of ODT that initially regressed after ovariectomy subsequently resumed progressive ovary-independent growth; this occurred with similar frequency in all age groups. In contrast to PGT, the incidence of SRT was significantly higher in rats given DMBA at 25 days of age (25D) than in those treated at 50D, 70D, or 200D, and the mean latent period was significantly shorter in the 25D and 50D groups. SRT did not occur in the 90D and 150D groups. Subsequent to an initial regression, 25%, 15%, and 40% of SRT regrew in the 25D, 50D, and 200D groups, respectively. Eighty percent, 50%, and 75% were ODT in the 25D, 50D, and 200D groups, respectively. The results indicate that age is a modifying factor in DMBA-induced mammary carcinogenesis in Lewis strain rats. It affected the number of SRT induced, the latent period of SRT development, and the number of tumors that regressed spontaneously. However, it does not confer significant or permanent refractoriness. (26 refs)

- 79-2039** Identification of 7,12-Dimethylbenz(a)anthracene Metabolites That Lead to Mutagenesis in Mammalian Cells. (Eng) Huberman, E. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 20014); Chou, M. W.; Yang, S. K. *Proc Natl Acad Sci USA* 76(2): 862-866; 1979.

An attempt was made to identify the metabolites that are responsible for 7,12-dimethylbenz(a)anthracene (DMBA) mutagenicity in mammalian cells and to determine by high-pressure liquid chromatography the type of DMBA metabolites that are produced in intact cells. The mutagenicity of DMBA and 11 of its enzymatically derived metabolites was tested with Chinese hamster V79 cells. The metabolites consisted of 7-hydroxymethyl-12-methylbenz(a)anthracene (I), 7-methyl-12-hydroxymethylbenz(a)anthracene (II), and 7,12-dihydroxymethylbenz(a)anthracene and 3 trans-3,4-diols, 2 trans-5,6-diols, and 3 trans-8,9-diols, all of which were

derived from DMBA or the hydroxymethyl derivatives. Mutations were characterized by resistance to ouabain (OB) and 6-thioguanine (TG). None of the tested metabolites were mutagenic in V79 cells, which do not metabolize polycyclic aromatic hydrocarbons. Therefore, mutagenesis in the V79 cells was tested in the presence of golden hamster cells capable of metabolizing polycyclic aromatic hydrocarbons (cell-mediated assay). In this assay, DMBA, metabolites I and II, and their trans-3,4-diols were mutagenic for both genetic markers, and the mutagenic response increased as a function of hydrocarbon dose. All other metabolites were either inactive or showed up to a four-fold higher mutation frequency than the untreated V79 cells for OB and TG resistance. The DMBA-trans-3,4-diol was the only metabolite that was more active than DMBA itself; at 0.05 μ M it was six to eight times more active than DMBA in inducing both OB and TG resistance. This diol was also mutagenic at 0.01 μ M. Mutagenesis by DMBA and the trans-3,4-diols was inhibited by 7,8-benzoflavone, an inhibitor of mixed-function oxidases. Analysis of DMBA metabolism in intact golden hamster cells indicated that DMBA-trans-3,4-diol is one of the major metabolites produced. DMBA-trans-3,4-diol may be metabolized to a diol-epoxide, presumably the trans-3,4-diol-1,2-epoxide, which may be a major reactive metabolite responsible for DMBA mutagenicity in mammalian cells. (58 refs)

- 79-2040** Systemic Two-Stage Carcinogenesis in the Epithelium of the Forestomach of Mice Using 7,12-Dimethylbenz(a)anthracene as Initiator and the Phorbol Ester 12-O-Tetradecanoylphorbol-13-acetate as Promoter. (Eng) Goerttler, K. (German Cancer Res. Center, Inst. Experimental Pathology, Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany); Loehrke, H.; Schweizer, J.; Hesse, B. *Cancer Res* 39(4): 1293-1297; 1979.

Systemic tumor initiation-promotion was investigated in the forestomach epithelium of female C57BL/6 mice. Fifty mice were treated intragastrically with a single dose of 7,12-dimethylbenz(a)anthracene (DMBA: 50 mg/kg) followed 1 wk later by repeated intragastric administration of the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA: 10 mg/kg 2x/wk for 35 wk). Forty-five of the 50 DMBA + TPA-treated animals developed tumors of the forestomach, compared with 0/50 untreated mice and 0/50 TPA-treated mice. Ten of 50 mice treated with DMBA alone developed forestomach tumors. DMBA + TPA-treated mice also developed tumors in other sites (skin, lip, thymus, lung, ovary, and hematopoietic system). The applicability of the two-stage experiment to the mouse forestomach is indicative of a preference of the DMBA-TPA combination for keratinizing epithelial tissues. (34 refs)

- 79-2041** Characteristics of Benzo(a)pyrene Metabolism by Kidney, Liver, and Lung Microsomal Frac-

tions from Rodents and Humans. (Eng) Prough, R. A. (Dept. Biochemistry, Univ. Texas Health Science Center at Dallas, Dallas, TX, 75235); Patrizi, V. W.; Okita, R. T.; Masters, B. S.; Jacobsson, S. W. *Cancer Res* 39(4): 1199-1206; 1979.

The kinetics of benzo(a)pyrene (BP) metabolism by microsomal fractions (MF) of liver and lung of rats, hamsters, and humans was studied by high-pressure liquid chromatography (HPLC). The formation of total BP metabolites (dihydrodiols, quinones, 4,5-oxides, and phenols) by liver MF from rats or hamsters pretreated with corn oil, phenobarbital (PB), or 3-methylcholanthrene (3-MC) was nonlinear with time beyond 2 min at low protein concentrations (0.3 mg/ml). However, human liver MF catalyzed BP metabolism that was linear up to 10 min at protein concentrations of 1-5 mg/ml. Hamster and rat lung MF metabolized BP at 0.5% of the rate of liver MF; the rate of metabolite formation was increased only by 3-MC pretreatment. The kinetics of metabolism by hamster and rat lung MF was linear up to 15 min. The MF from human kidney and lung were stable to freezing and had metabolic activities that were 40%-60% of those obtained with rodent lung. Liver activity, however, decreased 30%-40% during the first 14 hr of freezing. Human liver MF (unfrozen) had activities that were one-sixth those of the rodent liver. Persons who had ingested large doses of barbiturates before death had significantly higher levels of BP metabolism activity; no correlation was detected between liver or lung monooxygenase activity and smoking habits. Analysis of the product distribution of the benzo-ring metabolites showed that the human lung MF catalyzed the formation of a significantly higher proportion of benzo-ring metabolites than did other human or rodent organs, with the possible exception of hamster lung. (50 refs)

79-2042 Cell Sorter Analysis of Carcinogen Metabolites in Human Tissues. (Eng) Tyrer, H. W. (Becton, Dickinson Res. Center, Research Triangle Park, NC, 27709); Adams, L. A.; Tiffany, S. M.; O'Connell, J. P.; Cantrell, E. T. *J Histochem Cytochem* 27(1): 508-511; 1979.

A fluorescence-activated cell sorter (FACS-II) was used to study biochemical parameters in a heterogeneous population of cultured normal human lymphocytes. Some cultures were treated with 10 μ l benz(a)anthracene (BA). Cell sizes varied in phytohemagglutinin-activated cultures, with the larger cells containing more benzo(a)pyrene hydroxylase (BPOH) activity than the smaller cells. Among cells of a given size, BPOH activity was greater in those exposed to BA during culture than in untreated controls. When BA-induced lymphocytes were sorted into four subgroups according to size, the specific activity of ethoxyresorufin O-deethylation was greater in the larger cells than in the smaller cells. The technique of sorting before enzyme assay can be applied to cell types and enzyme reactions that cannot otherwise be measured directly. (10 refs)

79-2043 Benzo(a)pyrene Uptake by Human Plasma Lipoproteins In Vitro. (Eng) H. P. Shu (Donner Lab., Univ. California, Berkeley, CA, 94720); Nichols, A. V. *Cancer Res* 39(4): 1224-1230; 1979.

The in vitro uptake of benzo(a)pyrene (BP) by human plasma lipoproteins (LP) was studied using blood samples from healthy male donors (40-58 yr old). 14 C-BP was incubated in whole blood, plasma, or isolated LP fractions. BP distribution between plasma and RBC was estimated following sedimentation of RBC, and BP distribution in the major LP fractions was determined following ultracentrifugal fractionation of plasma. More than 70% of the BP was distributed in the plasma. Of the BP in plasma, <5% partitioned into the bulk of the plasma proteins [density (d) > 1.21 g/ml], >95% into plasma LP (d < 1.21 g/ml). BP distribution in normolipoproteinemic plasma was 29% in very-low-density, 57% in low-density, and 10% in high-density LP. The percentage of BP distribution among LP fractions was independent of the level of BP uptake by plasma. It was also independent of whether the incubation was conducted with total plasma that was subsequently fractionated into LP fractions or with isolated LP fractions. BP uptake by LP's was correlated with LP-total lipid volume for isolated very-low-density, low-density, and high-density LP's. BP incorporated into chylomicrons or isolated LP fractions transferred from chylomicron to LP and among LP, respectively. It is speculated that if BP is transported by the various LP classes in vivo, they may play a role in the cellular uptake of BP. Cellular uptake may involve simple partitioning of BP between the plasma LP's and the cell membrane lipid volume. Alternatively, cellular uptake of BP may proceed by a more specific process involving cell receptors. (24 refs)

79-2044 Preliminary Data on the Carcinogenic Effects of Adriamycin and Daunomycin in Male and Female Sprague-Dawley Rats. (Ita) Bucciarelli, E. (Cattedra di Anatomia Umana Normale, Universita degli Studi Urbino, Urbino, Italy); Provvienza, M.; Santori, P.; Vespasiani, G. *Lav Ist Anat Istol Patol Perugia* 38(2): 71-81; 1978.

The carcinogenicity of adriamycin and daunomycin (single 10-mg/kg doses in physiological saline solution iv) was studied in 1-mo-old virgin male and female Sprague-Dawley rats. Daunomycin induced breast tumors in 18/28 females (26 tumors: 24 adenocarcinomas and 2 fibroadenomas) and in 10/27 males (10 tumors: 9 adenocarcinomas and 1 fibroadenoma). The induction times were 36-213 days (median 80) in the females, and 39-196 days (median 83) in the males. Adriamycin induced 18 tumors (13 adenocarcinomas and 5 fibroadenomas) in 10/35 females after 90-206 days (median 135). No tumors developed in the 57 males. Three adenocarcinomas were found in 3/25 untreated control females after 114-360 days (median 220). The results suggest that hormonal factors are involved in the induction of breast tumors by adriamycin and daunomycin. (26 refs)

79-2045 Role of Inflammatory-Cell Proteases as Amplifiers of Chemical Promoters (Meeting Abstract). (Eng) Ranney, D. F. (Dept. Pathology, Univ. Texas Health Science Center, Dallas, TX, 75235); Quattrone, A. J. *Fed Proc* 38(3, part 2): 1073; 1979. (no refs)

79-2046 Inhibition of Functional and Morphological Differentiation of Cultured Mouse Myeloid Leukemia Cells by Tumor Promoters. (Eng) Kasukabe, T. (Dept. Chemotherapy, Saitama Cancer Center Res. Inst., Ina-machi, Kitaadachi-gun, Saitama-ken 362, Japan); Honma, Y.; Hozumi, M. *Gann* 70(1): 119-123; 1979.

The ability of 12-O-tetradecanoylphorbol 13-acetate (TPA) and related plant diterpenes to inhibit the induction of differentiation of biopotential mouse myeloid leukemia M1 cells into mature (phagocytic) macrophages and granulocytes was studied. First, the effects of TPA on the dexamethasone (DM)-induced phagocytic activity of M1 cells were determined. The phagocytic activity of M1 cells was reversibly inhibited by (DM: 10^{-7} M) plus TPA (1.6×10^{-8} M), but not by TPA alone. The degree of inhibition was dependent on the relative concentrations of both compounds. TPA (8×10^{-10} M) also inhibited 68% of the phagocytic activity of M1 cells induced by a 5% protein inducer. Phorbol 12,13-didecanoate (PDD: 1.6×10^{-7} M) was less a potent inhibitor of phagocytic activity than was TPA, and 4 α -phorbol 12,13-didecanoate and phorbol had no inhibitory effects. The inhibition of DM-induced phagocytic activity was not due to general cytotoxicity. TPA inhibited the induction of morphological differentiation of M1 cells by either DM or a 1% protein inducer. The data demonstrate that TPA and related plant diterpenes with tumor-promoting activity reversibly inhibit the induction of functional and morphological differentiation of M1 cells by DM or a protein inducer. (20 refs)

79-2047 Studies on a Possible Relationship Between Tumor Promotion and Glycosphingolipid Metabolism in Cultured Mammalian Cells (Meeting Abstract). (Eng) Moskal, J. R. (Dept. Biochemistry, Michigan State Univ., East Lansing, MI, 48824); Lockney, M.; Mason, P.; Sweeley, C. C. *Fed Proc* 38(3, part 1): 404; 1979. (no refs)

79-2048 Metabolism of 3-Methylcholanthrene (MC) and Alkylation of DNA (Meeting Abstract). (Eng) Bresnick, E. (Univ. Vermont, Burlington, VT, 05405); Tierney, B.; Eastman, A.; Grover, P.; Sims, P. *Fed Proc* 38(3, part 1): 683; 1979. (no refs)

79-2049 Ultrastructural Changes in Mouse Epidermis Following Treatment with 3-Methylcholanth-

rene (Meeting Abstract). (Eng) McDonald, T. F. (Dept. Anatomy, Medical Coll. Georgia, Augusta, GA); Cook, B. H.; Bresnick, E. E. *Anat Rec* 193(3): 619; 1979. (no refs)

79-2050 Effects of 3-Methylcholanthrene (3-MC) Treatment on Rat Liver Intermediary Metabolism (Meeting Abstract). (Eng) Kauffman, F. C. (Dept. Pharmacology, Univ. Maryland Sch. Medicine, Baltimore, MD); Evans, R. K.; Reinke, L. A.; Ballow, C.; Belinsky, S. A.; Thurman, R. G. *Fed Proc* 38(3, part 1): 846; 1979. (no refs)

79-2051 The Mutagenic Activity of Halogenated Compounds Found in Chlorinated Drinking Water. (Eng) Simmon, V. F. (Microbial Genetics Program, Stanford Res. Inst. International, Menlo Park, CA, 94025); Tardiff, R. G. *Water Chlorination* 2: 417-431; 1978.

The mutagenic activities of 22 halogenated compounds found in chlorinated drinking water were determined using the Ames *Salmonella*/microsome procedure with *S. typhimurium* strains TA1535 and TA100. Two known carcinogens, carbon tetrachloride and chloroform, were not mutagenic in this system, probably because mutagenic metabolites were formed in insufficient amounts or they were so unstable that they did not survive long enough to penetrate the bacteria and interact with the DNA. Known carcinogens that were mutagenic were vinyl chloride, vinylidene chloride, 1,2-dichloroethane, 1,1,2-trichloroethylene, bis(2-chloroethyl)ether, methyl iodide, and bromoform. Mutagenic activity was also observed with bromodichloromethane, chlorodibromomethane, methylene bromide, bromochloromethane, methylene chloride, methyl bromide, methyl chloride, 2-chloropropane, 1-chloropropene, bis(2-chloroisopropyl)ether, n-butyl bromide, t-butyl bromide, and s-butyl bromide. The results indicate that the number and amount of alkyl halides in potable water should be reduced to lessen possible health hazards. (20 refs)

79-2052 Photochemical and Biological Implications of the Atmospheric Reactions of Amines and Benzo(a)pyrene. (Eng) Pitts, J. N. (Statewide Air Pollution Res. Center and Dept. Chemistry, Univ. California, Riverside, CA, 92521). *Phil Trans R Soc Lond* 290(1376): 551-576; 1979.

The reactions of benzo(a)pyrene (BP) and its nonmutagenic isomer perylene in simulated and real urban atmospheres, the reactions of mixtures of simple aliphatic amines and nitrogen oxides in air containing traces of nitrous acid (HONO), and the mutagenicity of ambient urban particles were studied. The Ames assay was used to screen for mutagenic activity in particulate samples from urban atmospheres. The samples exhibited frameshift but not base-pair substitution mutations,

and there was no requirement for metabolic activation. Exposure of BP in the dark to the gases in ambient smog resulted in the formation of direct-acting frameshift mutagens with no base-pair substitution activity. Perylene and pyrene formed mutagens under similar conditions. These reactions might account for part of the carcinogenicity of organic particulates collected from smog and exhausts of spark ignition and diesel engines. At < 1 ppm, diethylamine and triethylamine (DEA and TEA) readily formed photochemical smog in outdoor chambers. Small but significant amounts of diethylnitrosamine (DEN) were formed in the dark from DEA, but they were destroyed in sunlight. In contrast, DEN was initially formed upon irradiation of TEA-nitrogen oxide mixtures and then it photodecomposed. Other significant nitrogenous compounds formed in sunlight include dialkylnitramines and substituted amides; small amounts of acetamide were present in the particulate phase from DEA and TEA. (131 refs)

79-2053 Metabolism of Benzo(a)pyrene by Multinucleated Giant Cells. (Eng) Bockman, D. E. (Dept. Anatomy, Medical Coll. Georgia, Augusta, GA, 30902); Black, O.; Webster, P. D. *J Reticuloendothel Soc* 25(1): 39-47; 1979.

The ability of benzo(a)pyrene (BP) crystals (1 or 5 mg) implanted on the surface of pancreas for periods of 1-8 mo to induce pancreatic tumors was studied in 123 male and female Long-Evans rats. Yellowish granular deposits were observed in the regions of the original implant at all times. Large complexes composed of multinucleated giant cells, macrophages, and a narrow peripheral band of connective tissue cells and fibers were arranged around the crystals. The giant cells occupied spaces previously occupied by other BP crystals, and they contained numerous organelles that were usually dispersed uniformly close to the cell membrane bordering the central BP crystals. Extremely small bits of BP crystal were also seen deeper in the cytoplasm of these cells, and the periphery of each giant cell was frequently characterized by elaborate interdigitating cellular processes bordering areas of connective tissue. Carcinomas were not observed, but acute and chronic reactive cells were frequently present. The implant region sometimes became adherent to another organ. Occasionally, an abscess developed. The pancreas frequently showed chronic inflammation and accumulations of tubular complexes similar to those present during tumor induction by 7,12-dimethylbenz(a)anthracene. (16 refs)

79-2054 3,4-Benzopyrene and Perylene in Mussels, *Mytilus* SP. from the Laguna Veneta, Northeast Italy. (Eng) Fossato, V. U. (Istituto di Biologia del Mare, Consiglio Nazionale delle Ricerche, Riva Sette Martiri 1364/A, Venezia 30122, Italy); Nasci, C.; Dolci, F. *Mar Environ Res* 2(1): 47-53; 1979.

Mussels collected bimonthly during July 1975 to November 1976 from the Laguna Veneta in northeastern Italy and the adjacent Adriatic sea were analyzed for benzo(a)pyrene (BP) and perylene (Pe) levels. Mean concentrations of BP and Pe were generally in the range 12.0-135.1 and 1.5-16.9 $\mu\text{g/kg}$ dry wt, respectively, but values as high as 327 $\mu\text{g/kg}$ for BP and 71 $\mu\text{g/kg}$ for Pe were obtained. The highest concentrations were usually found in mussels taken from waters adjacent to the industrial port area and within the city of Venice and in an area limited to the fishing port of Chioggia. The lowest levels were found in mussels from the Adriatic Sea and in the central basin of the Laguna Veneta, areas furthest from the industrial and urban areas. The ratio of BP to Pe was always close to 7.3, indicating a common major source for these pollutants (most probably associated with the combustion of fossil fuels). A gradient of contamination was demonstrated, with concentrations decreasing with distance from the source of pollution. Similar results were obtained in a previous study of aliphatic hydrocarbon contamination of mussels in this area. Max concentrations of BP and Pe were found in mussels taken in May and July. The degrees of contamination observed probably do not represent a serious human health hazard. (20 refs)

79-2055 Primary and Secondary Metabolism of Benzo(a)pyrene by Marine Fish (Meeting Abstract). (Eng) von Hofe, E. H. (Sch. Medicine, Univ. Southern California, Los Angeles, CA, 90033); Gehly, E. B.; Puffer, H. W. *Fed Proc* 38(3, part 1): 692; 1979. (no refs)

79-2056 Binding of Metabolically Activated Benzo(a)pyrene to DNA Catalyzed by Starry Flounder (*Platichthys stellatus*) Liver Extract (Meeting Abstract). (Eng) Varanasi, U. (Environmental Conservation Div., Northwest & Alaska Fishing Center, Seattle, WA, 98112); Gmur, D. J. *Fed Proc* 38(3, part 1): 662; 1979. (no refs)

79-2057 A Study of Biological Activity of Polycyclic Aromatic Hydrocarbons and Related Compounds by a Bacteriophage System and of Binding and Inactivation of Phage ϕX174 DNA by Benzo[a]pyrene-7,8-dihydrodiol (Meeting Abstract). (Eng) Hsu, W. T. (Franklin Mclean Memorial Res. Inst., Ben May Lab. Cancer Res., Univ. Chicago, Chicago, IL, 60637); Sagher, D.; Lin, E. J.; Harvey, R. G.; Weiss, S. B. *Fed Proc* 38(3, part 1): 663; 1979. (no refs)

79-2058 Recovery of Benzo(a)pyrene, 3-Methylcholanthrene and Their Metabolites in Rat Saliva after ip Injection (Meeting Abstract). (Eng) Snyder, W. (Dept. Biochemistry, New York Univ. Dental Center, New

York, NY, 10010); Guttentplan, J. B. *Fed Proc* 38(3, part 1): 660; 1979. (no refs)

- 79-2059** The Metabolic Activation of Benzo(a)pyrene and 9-Hydroxybenzo(a)pyrene by Liver Microsomal Fractions. (Eng) Lubet, R. A. (Dept. Biochemistry, Univ. Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, TX, 75235); Capdevila, J.; Prough, R. A. *Int J Cancer* 23(3): 353-357; 1979.

The microsome-mediated *Salmonella typhimurium* assay was used to compare the metabolic activation of benzo(a)pyrene (BP) and 9-hydroxybenzo(a)pyrene (9-hydroxy-BP) to mutagenic and alkylating moieties by liver microsomes from 5,6-benzoflavone (BF)-pretreated male Sprague-Dawley CD rats. 9-Hydroxy-BP was 1.75 times more mutagenic than BP in this system. Studies of the binding of BP and 9-hydroxy-BP to exogenous calf thymus DNA in the presence of microsomes from BF-pretreated rats showed that 9-hydroxy-BP was significantly more effective than BP, yielding almost six times more DNA-bound hydrocarbon. Trichloropropene-2,3-oxide increased the mutagenicity of BP by almost 60% and increased the microsome-mediated binding of BP to DNA by 100%. However, it had little effect on the mutagenicity of, or DNA alkylation by, 9-hydroxy-BP. BF substantially inhibited both BP- and 9-hydroxy-BP-mediated mutagenesis and alkylation in a concentration-dependent fashion. (24 refs)

- 79-2060** Effect of Benzo(a)pyrene on Intermediary Metabolism in Isolated Perfused Rat Livers (Meeting Abstract). (Eng) Reinke, L. A. (Dept. Pharmacology, Univ. North Carolina, Chapel Hill, NC); Ballow, C.; Belinsky, S. A.; Evans, R. K.; Kauffman, F. C.; Thurman, R. G. *Fed Proc* 38(3, part 1): 661; 1979. (no refs)

- 79-2061** Correspondence Between the Fluorescence of Monomeric Benzo(a)pyrene Carcinogens Complexed by DNA and Their Fluorescence in Various Solvents (Meeting Abstract). (Eng) Capomacchia, A. C. (Pharmaceutics Dept., Sch. Pharmacy, Univ. Georgia, Athens, GA, 30602); White, F. L.; Sobol, T. L. *Fed Proc* 38(3, part 1): 691; 1979. (no refs)

- 79-2062** Covalent Binding of Benzo(a)pyrene Diol Epoxide (anti) to Rauscher Leukemia Virus Proteins and RNA In Situ (Meeting Abstract). (Eng) Harris, R. M. (Worcester Foundation for Experimental Biology, Shrewsbury, MA, 01545); Kupfer, D.; Luftig, R. B. *Fed Proc* 38(3, part 1): 813; 1979. (no refs)

- 79-2063** Uptake and Excretion of Benzo(a)pyrene and Its Metabolites by the Rat Pancreas. (Eng) Iqbal, Z. M. (Sch. Public Health, Univ. Illinois at Medical Center, P.O. Box 6998, Chicago, IL, 60680); Yoshida, A.; Epstein, S. S. *Drug Metab Dispos* 7(1): 44-48; 1979.

The uptake and excretion of benzo(a)pyrene (BP) in the rat pancreas were investigated and compared with uptake and excretion in the liver and bile. Following the iv administration of [³H]BP (0.9 ml plasma containing 9.99×10^7 disintegrations/min) to male Sprague-Dawley rats, uptake of radioactivity by the pancreas (per gram of tissue) was approx 16% of that in the liver. At 5 min following administration, unmetabolized BP in the pancreas, liver, and blood constituted 79%, 50%, and 49% of total BP uptake, respectively. The total uptake and unmetabolized BP in these tissues declined in a biphasic manner over the 2-hr observation period, during which only 0.30% of the total administered dose was excreted in pancreatic juice, compared with 39% in bile. All radioactivity in pancreatic juice and bile was due to polar BP metabolites, including 3-hydroxy-BP. Methylcholanthrene pretreatment (20 mg/kg, ip) induced a significant increase ($p < 0.005$) in biliary, but not pancreatic, excretion of radioactivity. The administration of secretin and pancreozymin caused a twofold increase ($p < 0.001$) in pancreatic, but not biliary, radioactivity. It appears that pancreatic acinar and ductal cells could easily be exposed to carcinogenic BP metabolites of hepatic origin either during biliary excretion or following transportation to the pancreas by the blood. Accumulation of carcinogenic metabolites in the pancreas, combined with prolonged cellular exposure, may be relevant to an understanding of BP carcinogenicity in the rat. (36 refs)

- 79-2064** Metabolism of Chemical Carcinogens by Cultured Colon (Meeting Abstract). (Eng) Autrup, H. (Human Tissue Studies Section, Lab. Experimental Pathology, NCI, Bethesda, MD, 20014); Essigmann, J. M.; Harris, C. C. *Fed Proc* 38(3, part 2): 1073; 1979. (no refs)

- 79-2065** Induction of Carcinoma in Rat Tracheal Epithelium by Long-Term Low Dose Exposure to Benzo(a)pyrene (Meeting Abstract). (Eng) Lane, B. P. (State Univ. New York, Health Science Center, Stony Brook, NY, 11594); Weinhold, C. L. *Fed Proc* 38(3, part 2): 1450; 1979. (2 refs)

- 79-2066** Ambient Temperature Modifies the Course of Benzo(a)pyrene Skin Tumors in Mice (Meeting Abstract). (Eng) Weiss, H. S. (Dept. Physiology, Ohio State Univ., Columbus, OH, 43210); Kerr, K. M.; Weisbrode, S. E.; Daniel, F. B.; Pitt, J. F.; Zeid, A. M.; Wilson, R. H.; Hakaim, A. G.; Schniegenberg, K. J. *Fed Proc* 38(3, part 2): 1450; 1979. (no refs)

- 79-2067 Benzo[a]pyrene Metabolism by Hepatic and Extrahepatic Tissues in Streptozotocin-diabetic Rats.** (Eng) Stohs, S. J. (Dept. Biomedical Chemistry, Coll. Pharmacy, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105); Reinke, L. A.; Hassing, J. M.; Rosenberg, H. *Drug Metab Dispos* 7(1): 49-51; 1979.

Microsomal benzo(a)pyrene (BP) metabolism was studied in the liver, lung, kidney, and adrenal gland of Sprague-Dawley female rats 7 or 10 days following the induction of diabetes in these animals with streptozotocin (60 mg/kg, iv). BP metabolism in hepatic microsomes was increased by 75% compared with that in controls ($p < 0.05$), and cytochrome P-450 levels were similarly increased ($p < 0.005$). BP monooxygenase activity in the intestinal microsomes was approx 2.7 times that of control rats ($p < 0.005$), whereas BP monooxygenase activity in the lung microsomes was decreased by 40% ($p < 0.005$). No significant changes in BP metabolism were observed in the kidney or adrenal tissues of diabetic animals. Changes in hepatic, intestinal, and lung microsomal enzyme levels normalized following insulin administration, suggesting that altered BP metabolism results from the diabetic state and not as a direct effect of streptozotocin. The dramatic reduction in BP metabolism by lung microsomes, in contrast to the stimulatory effect of diabetes on the BP monooxygenase activity in the intestine and liver, suggests that there are separate regulatory mechanisms for BP monooxygenase in lung and liver. The lung metabolism of drugs, endogenous substrates, and other xenobiotics may be impaired in the diabetic state. (31 refs)

- 79-2068 Genetic Differences in the Binding of Benzo(a)-pyrene Metabolites to DNA in the Mouse.** (Eng) Boobis, A. R. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20014); Kouri, R. E.; Nebert, D. W. *Cancer Detect Prev* 2(1): 83-111; 1979.

Genetic differences in the binding of benzo(a)pyrene (BP) metabolites to DNA were assessed in female C3H, C57BL/6, and DBA/2 mice. When the mice were inoculated sc with 150 μ g BP, the carcinogenic index (CI: % tumor incidence/av latency, $\times 100$) for C3H was > 5 times greater than that for C57BL/6 and about 15 times greater than that for DBA/2. Sephadex LH20 column chromatography of an enzyme digest of DNA with 3 H-BP metabolites bound during in vitro incubation with hepatic microsomes from 3-methylcholanthrene-treated mice of all three strains revealed that nine peaks, representing BP metabolites bound to DNA nucleosides (NS), could be identified reproducibly. When C3H or C57BL/6 was compared with DBA/2, a positive general correlation was found between CI in vivo and the size of 8/9 peaks, hepatic aryl hydrocarbon hydroxylase activity, and total hepatic cytochrome P-450 content. Peaks D, E, H, and I demonstrated relative differences among the three strains that were in the same direction as the CI; ie, the C3H peaks were greater than the C57BL/6 peaks, and both were consid-

erably greater than the DBA/2 peaks. However, no such correlation was found when C3H was compared with C57BL/6. Hence, the total quantity of NS-BP metabolite complexes in each of the nine peaks was not necessarily associated with the CI. A defect in the general immune competence of C3H may be an important factor in its markedly increased susceptibility to BP-initiated tumorigenesis, compared with C57BL/6. C3H has the H-2k allele, C57BL/6 the H-2b allele; differences in these alleles have been found to be related to susceptibility to viral-induced tumors and perhaps immune competence as well. Peak G was associated, at least in part, with complexes involving BP 4,5-oxide, whereas the other eight peaks were associated predominantly with metabolites formed by cytochrome P₁-450 rather than other forms of P-450. Interestingly, in view of the CI's, no peak from C3H was greater than twice that of C57BL/6. (65 refs)

- 79-2069 Fluorescence Study of the Physico-chemical Properties of a Benzo(a)pyrene 7,8-Dihydrodiol 9,10-Oxide Derivative Bound Covalently to DNA.** (Eng) Prusik, T. (Chemistry Dept., New York Univ., New York, NY, 10003); Geacintov, N. E.; Tobiasz, C.; Ivanovic, V.; Weinstein, I. B. *Photochem Photobiol* 29(2): 223-232; 1979.

An in vitro system that mimics exactly the stereoselective in vivo binding of benzo(a)pyrene (BP) to DNA was developed. Using fluorescence lifetime and quenching studies, it was shown that the 7,8-dihydrodiol 9,10-oxide benzo(a)pyrene molecule bound to native DNA is definitely not intercalated in the DNA helix, in contrast to BP physically bound to DNA. (29 refs)

- 79-2070 Effect of *Nocardia Rubra* Cell-Wall Skeleton on the Induction of Lung Cancer in ACI/N Rats.** (Eng) Namba, M. (Third Dept. Internal Medicine, Osaka Univ. Medical Sch., Fukushima 1-1-50, Fukushima-ku, Osaka 553, Japan); Yoshimoto, T.; Ogura, T.; Hirao, F.; Azuma, I.; Yamamura, Y. *Gann* 70(1): 55-62; 1979.

The effect of oil-attached *Nocardia rubra* cell-wall skeletons (NR-CWS: 7 sc injections of 100 μ g given at 2-wk intervals) on the induction of lung tumors in ACI/N rats by benzo(a)pyrene (BP: 3 mg/wk given intratracheally for 15 wk) + ferric oxide (FO: 3 mg/wk given intratracheally for 15 wk) was determined. BP + FO induced primarily squamous cell carcinoma and squamous cell carcinoma + fibrosarcoma in 71.4% of the treated rats. Treatment with NR-CWS significantly reduced the lung tumor incidence in the BP + FO-treated rats to 48.0% and prolonged the latent period for tumor induction. The first tumor in the group treated with BP + FO appeared at 15 wk, whereas the first tumor in the group treated with BP + FO and NR-CWS did not appear until 31 wk. No fibrosarcomas were observed in the rats treated with BP + FO and NR-CWS. (28 refs)

79-2071 Neoplastic Effects of Oral Administration of (\pm)-trans-Dihydroxy-7,8-dihydrobenzo[a]pyrene and Their Inhibition by Butylated Hydroxyanisole. (Eng) Wattenberg, L. W. (Dept. Lab. Medicine and Pathology, Univ. Minnesota Medical Sch., Minneapolis, MN, 55455); Jerina, D. M.; Lam, L. K.; Yagi, H. *J. Natl Cancer Inst* 62(4): 1103-1106; 1979.

The neoplastic effects of administration of benzo[a]pyrene (BP) and (\pm)-trans-7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene (BP 7,8-dihydrodiol) by oral intubation of noninbred female Ha:ICR mice have been determined. Under the experimental conditions, BP induced papillomas of the forestomach. BP 7,8-dihydrodiol also induced papillomas of the forestomach and was more potent than BP. In addition, administration of BP 7,8-dihydrodiol caused a large number of pulmonary adenomas and lymphomas. Butylated hydroxyanisole (BHA) added to the diet at a concentration of 5 mg/g inhibited BP-induced neoplasia of the forestomach. BHA also inhibited neoplasia of the forestomach, lungs, and lymphoid tissues that was caused by administration of BP 7,8-dihydrodiol. These data suggest that the inhibitory effect of BHA on BP carcinogenesis may entail events that occur subsequent to the formation of BP 7,8-dihydrodiol. (30 refs)

79-2072 Aryl Hydrocarbon Hydroxylase Activity in Mice Fed Benzo(a)pyrene and Varying in Source and Concentration of Protein (Meeting Abstract). (Eng) Truex, C. R. (Univ. Illinois, Urbana, IL, 61801); Clinton, S. K.; Visek, W. J. *Fed Proc* 38(3, part 1): 691; 1979. (1 ref)

79-2073 Aryl Hydrocarbon [Benzo(a)pyrene] Hydroxylase in Rat Mammary Tissue During Pregnancy and Lactation. (Eng) Fysh, J. M. (Dept. Biology, Univ. Windsor, Windsor, Ontario N9B 3P4, Canada); Okey, A. B. *Can J Physiol Pharmacol* 57(1): 112-117; 1979.

Aryl hydrocarbon hydroxylase (AHH) activity in microsomes from mammary tissue and liver was measured throughout the course of pregnancy and lactation in Sprague-Dawley rats to determine if altered capacity to metabolize polycyclic aromatic hydrocarbons (PAH's) could explain the resistance of rats to tumor induction during this period. Basal constitutive AHH activity in mammary tissue and liver of untreated rats did not change significantly during pregnancy or lactation. In rats injected with β -naphthoflavone (BNF: 80 mg/kg ip), AHH activity in liver microsomes increased 25-fold over basal levels and remained relatively constant throughout pregnancy and lactation. In mammary tissue, however, the induction of AHH by BNF increased from 12- to 86-fold when expressed per unit protein and from 19- to 106-fold when expressed per unit DNA. Since basal AHH and its inducibility in liver are not altered during pregnancy or lactation, it is

unlikely that changes in the hepatic metabolism of PAH's account for the great resistance of pregnant and lactating rats to PAH induction of mammary tumors. It is suggested that the local metabolism of PAH's by mammary tissue may be important in contributing to the resistance of these rats to tumor induction. The balance between local activation and detoxification of PAH's by AHH in mammary tissue during different physiological states is important in determining susceptibility to carcinogenesis. (13 refs)

79-2074 Antagonistic Action Between Cyclic Adenosine 3':5'-Monophosphate and Estrogen in Rat Mammary Tumor Growth Control. (Eng) Cho-Chung, Y. S. (Lab. Pathophysiology, NCI, NIH, Bethesda, MD, 20014). *Cancer Res* 38(11, part 2): 4071-4075; 1978.

Evidence that the regulation of hormone-dependent rat mammary tumor growth may depend on the antagonistic action between estrogen (E) and cyclic AMP (cAMP) was obtained by measuring (1) E- and cAMP-binding activities in biopsy specimens of 35 7,12-dimethylbenz(a)anthracene (DMBA)-induced or transplanted Sprague-Dawley rat mammary carcinomas and (2) the tumor responses to host ovariectomy (Ov-x). When hormone-dependent DMBA tumors underwent growth arrest following Ov-x or dibutyl cAMP (dbcAMP) treatment (10 mg/day, sc), the binding activities changed. Three days after either treatment, cAMP binding increased five- and twofold in the tumor nuclei and cytosols, respectively, but nuclear and cytoplasmic E binding decreased by 70% and 25%, respectively. These changes were detectable within 1 day, and they were reversed when tumor growth resumption was induced by injection of estradiol valerate or cessation of dbcAMP treatment. When the tumors failed to regress after either treatment, the change in both binding activities did not occur. Concomitant with the increase in cAMP binding in the regressing tumors was an increase in protein kinase activity and cAMP level. Further evidence of an interrelationship between cAMP and E at the nuclear level, both in vivo and in vitro, was shown by the stimulation and prevention of endogenous phosphorylation of nuclear proteins, identified as regression-associated proteins, by cAMP and E, respectively. The inverse relationship between cAMP and E binding was closely related to the hormone dependence of tumor growth. Thus, the integrity of both cAMP-binding proteins and E receptors is probably essential for the control of hormone-dependent mammary tumor growth. (30 refs)

79-2075 The Effects of Jejuno-Ileal Resection on Colonic Mucosal Cytochrome P450 (P450)-dependent Enzymes (Meeting Abstract). (Eng) Correia, M. A. (Univ. California, San Francisco, CA, 94143); Olson, S.; Deveney, C. *Fed Proc* 38(3, part 1): 692; 1979. (no refs)

- 79-2076 Rat Hepatic Nuclear Cytochrome P-450 and Epoxide Hydrase in Membranes Prepared by Two Methods: Similarities with the Microsomal Enzymes.** (Eng) Mukhtar, H. (Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709); Elmamlouk, T. H.; Philpot, R. M.; Bend, J. R. *Mol Pharmacol* 15(1): 192-196; 1979.

DNase digestion and sucrose density centrifugation experiments showed that rat hepatic nuclear (Nu) and microsomal (Ms) cytochrome P-450 forms cannot be distinguished on the basis of their CO difference spectra and that the inductive effects of phenobarbital and 3-methylcholanthrene on Nu and Ms cytochrome P-450 and epoxide hydrase (EH) are similar. The similar characteristics of the hepatic Nu and Ms monooxygenase (MO) systems and EH suggest a common biogenesis. The presence of significant MO and EH activities in the nucleus is consistent with a role for this organelle in the bioactivation of environmental pollutants to carcinogens and/or mutagens. (30 refs)

- 79-2077 Senescent Changes in Mouse Hepatic Aryl Hydrocarbon Hydroxylase (Meeting Abstract).** (Eng) Birnbaum, L. S. (Masonic Medical Res. Lab., Utica, NY, 13503); Baird, M. B. *Fed Proc* 38(3, part 1): 658; 1979. (1 ref)

- 79-2078 Wheat Bran and the Induction of Intestinal Aryl Hydrocarbon Hydroxylase (Meeting Abstract).** (Eng) Clinton, S. K. (Univ. Illinois, Urbana, IL, 61801); Edes, T. E.; Truex, C. R.; Visek, W. J. *Fed Proc* 38(3, part 1): 713; 1979. (1 ref)

- 79-2079 Maturational Changes in Adrenal Xenobiotic Metabolism in Male and Female Guinea Pigs.** (Eng) Pitrolo, D. A. (Dept. Physiology and Biophysics, West Virginia Univ. Medical Center, Morgantown, W. Va., 26506); Rumbaugh, R. C.; Colby, H. D. *Drug Metab Dispos* 7(1): 52-56; 1979.

Changes in hepatic and adrenal enzyme activities with age and sex were studied in strain 2 guinea pigs. Hepatic microsomal protein and hepatic and adrenal cytochrome P-450 concentrations plus adrenal 21-hydroxylase activity did not vary with age or sex. Adrenal microsomal protein concentration, adrenal NADPH-cytochrome c reductase activity, and the rates of adrenal benzo(a)pyrene (BP) and ethylmorphine (EM) metabolism increased with age, but microsomal protein and NADPH-cytochrome c reductase did not vary with sex. BP and EM metabolism were significantly higher in males > 50 days of age than in females of the same age. Hepatic NADPH-cytochrome c reductase activity decreased with age, as did hepatic BP and EM metabolism; there were no

sex differences in these activities. Levels of microsomal protein and microsomal cytochrome P-450, NADPH-cytochrome c reductase activity, and BP and EM metabolism were greater in the adrenals than in the liver. The data suggest that opposite changes occur in adrenal and hepatic xenobiotic metabolism as a function of aging, resulting in substantially greater adrenal than hepatic activity in sexually mature animals, and that adrenal microsomal drug and steroid metabolism are independently regulated. (39 refs)

- 79-2080 Lack of Inducibility of Lymphocyte Aryl Hydrocarbon Hydroxylase in Acute Leukemia of Childhood (Meeting Abstract).** (Eng) Blumer, J. L. (Case Western Reserve Univ., Cleveland, OH, 44106); Dunn, R.; Gross, S. *Fed Proc* 38(3, part 1): 658; 1979. (no refs)

- 79-2081 Aryl Hydrocarbon Hydroxylase in Cultured Lymphocytes of Twins.** (Eng) Paigen, B. (Dept. Molecular Biology, Roswell Park Memorial Inst., Buffalo, NY, 14263); Ward, E.; Steenland, K.; Houten, L.; Gurtoo, H. L.; Minowada, J. *Am J Hum Genet* 30(5): 561-571; 1978.

Aryl hydrocarbon hydroxylase (AHH) activity was measured in cultured lymphocytes of 18 monozygotic and 30 dizygotic twin pairs as part of a series of studies to determine whether there is a genetic polymorphism for AHH and whether the polymorphism affects cancer risk. Monozygotic twin pairs had strikingly similar basal and induced AHH activities and inducibility ratios (induced/basal). The data indicated that basal and induced AHH activity and AHH inducibility are heritable traits. Most of the dizygotic twins also had similar values, so that most of the variance used in determining heritability was contributed by only a few dizygotic pairs: 2 pairs contributed 61% of the variance for basal AHH, 4 contributed 70% for induced AHH, and 2 contributed 62% for AHH inducibility. The similarity of values for most dizygotic twins is consistent with the hypothesis that only one or a very few polymorphic genes determine AHH activities and inducibility. (29 refs)

- 79-2082 Aryl Hydrocarbon Hydroxylase Inducibility is not Altered in Bladder Cancer Patients or Their Progeny.** (Eng) Paigen, B. (Dept. Molecular Biology, Roswell Park Memorial Inst., Buffalo, NY, 14263); Ward, E.; Steenland, K.; Havens, M.; Sartori, P. *Int J Cancer* 23(3): 312-315; 1979.

To determine the possible influence of aryl hydrocarbon hydroxylase (AHH) on susceptibility to bladder cancer in humans, AHH inducibility was measured in the cultured lymphocytes of 16 apparently cancer-free patients who had undergone resection for bladder cancer, 53 progeny of bladder cancer patients, and matched controls. The progeny and

matched controls showed similar distributions of AHH inducibility except for a possible increase in the number of progeny at the high end of the AHH inducibility range. This apparent increase was not significant. There were no significant differences in AHH inducibility among progeny when those whose parents developed bladder cancer below 60 yr of age were compared with those whose parents developed bladder cancer after 60 yr of age, or when progeny with strong family histories of cancer were compared with controls with no family history of cancer. The basal and induced levels of AHH activity did not vary between progeny and controls, and the distribution of AHH activity was comparable for patients with bladder cancer and their matched controls. Thus, AHH activity of inducibility does not appear to be a major determinant of bladder cancer risk in humans. (24 refs)

79-2083 Vitamin A Inhibits Mutagenicity by 2-Fluoreneamine in *Salmonella typhimurium* (Meeting Abstract). (Eng) Baird, M. B. (Masonic Medical Res. Lab., Utica, NY, 13501); Birnbaum, L. S. *Fed Proc* 38(3, part 1): 701; 1979. (no refs)

79-2084 Citral Promotes BW10232 Tumor Growth: Vitamin A Antagonizes This (Meeting Abstract). (Eng) Seifter, E. (Albert Einstein Coll. Medicine, Bronx, NY); Rettura, G.; Liu, S.; Levenson, S. M. *Fed Proc* 38(3, part 1): 714; 1979. (1 ref)

79-2085 N-(4-Hydroxyphenyl)retinamide, a New Retinoid for Prevention of Breast Cancer in the Rat. (Eng) Moon, R. C. (IIT Res. Inst., Chicago, IL, 60616); Thompson, H. J.; Becci, P. J.; Grubbs, C. J.; Gander, R. J.; Newton, D. L.; Smith, J. M.; Phillips, S. L.; Henderson, W. R.; Mullen, L. T.; Brown, C. C.; Sporn, M. B. *Cancer Res* 39(4): 1339-1346; 1979.

A comparison was made of the toxicity and inhibition of breast cancer induction of N-(4-hydroxyphenyl)-all-trans-retinamide (HPR) and retinyl acetate (RA) in Sprague-Dawley rats. HPR was markedly less toxic than RA when given to rats over 2 wk (30.4 or 45.6 micromoles, 5x/wk po) or 6 mo (1 or 2 millimoles/kg of diet). HPR was an effective agent for the inhibition of breast cancer induction by N-nitroso-N-methylurea (15 or 50 mg/kg iv, 2x, 7 days apart) but it was not as potent as RA in this respect. High-pressure liquid chromatographic analyses of liver and breast extracts from rats treated with retinoids for 6 mo showed high concentrations of HPR and its metabolites in breast tissue without any measurable accumulation in the liver or evident liver toxicity. Chronic feeding of RA, however, caused marked deposition of retinyl esters in the liver and severe hepatotoxicity. Evaluation of whole mounts of mammary glands from rats treated with the

retinoids for 182 days showed that both RA and HPR had a marked antiproliferative effect on mammary epithelium. It is suggested that HPR, because of its lesser toxicity, is a superior agent for the prevention of breast cancer than RA. (22 refs)

79-2086 Effect of Time of Initiating Retinoid Treatment on the Inhibition of Urinary Bladder Carcinogenesis in the Rat (Meeting Abstract). (Eng) Becci, P. J. (IIT Res. Inst., Chicago, IL, 60616); Thompson, H. J.; Grubbs, C. J.; Brown, C. C.; Sporn, M. B.; Moon, R. C. *Lab Invest* 40(2): 240; 1979. (no refs)

79-2087 Mammary Carcinomas and Liver Adenomas in Mice Treated with Retinyl Acetate (Meeting Abstract). (Eng) Maiorana, A. (NIH, Bethesda, MD, 20014); Gullino, P. M. *Fed Proc* 38(3, part 2): 1450; 1979. (no refs)

79-2088 Effect of Vitamin A Deficiency on Rat Hepatic and Colon Epoxide Hydrase. (Eng) Adekunle, A. A. (Biochemistry Dept., Univ. Ibadan, Ibadan, Nigeria); Campbell, T. C.; Campbell, S. C. *Experientia* 35(2): 241-242; 1979.

Metabolic studies of the conversion of 7-³H-styrene oxide to 7-³H-styrene glycol by epoxide hydrase were performed with liver microsomes and homogenized colon mucosal linings prepared from male weanling Sprague-Dawley-derived rats fed a corn-based diet without vitamin A or on a diet supplemented with 5 mg of vitamin A palmitate/kg diet for 45 days. The colon tissue of deficient animals exhibited a significantly higher (39%) value of V_{max} than the same tissue from supplemented animals. The liver tissue of deficient animals had a lower (8%) V_{max} value than the same tissue from supplemented animals. This implies that under vitamin A supplementation, free substrate would be available for complementation with RNA, DNA, and tissue protein but that the higher K_m value at which the reaction proceeds in vitamin A-supplemented animals may reduce such possibilities. The reverse of this interpretation as applied to vitamin A-deficient animals may explain carcinogenesis in these animals under drug metabolism. (26 refs)

79-2089 Studies on the Metabolism of Diethylstilbestrol (DES) by Rat Liver Microsomes to p-Hydroxypropioophenone (Meeting Abstract). (Eng) Laskowski, P. T. (Dept. Biochemistry, Northwestern Univ., Chicago, IL, 60611); Chen, C. *Fed Proc* 38(3, part 1): 663; 1979. (1 ref)

79-2090 Development of DES-Associated Clear-Cell Carcinoma: The Importance of Regular Screen-

ing. (Eng) Anderson, B. (Dept. Obstetrics & Gynecology, New England Medical Center Hosp., 171 Harrison Ave., Boston, MA, 02111); Waring, W. G.; Edinger, D. D.; Small, E. C.; Netland, A. T.; Safaii, H. *Obstet Gynecol* 53(3): 293-299; 1979.

A case is presented that is believed to represent the first reported instance of clear cell adenocarcinoma of the vagina in a diethylstilbestrol (DES) exposed (in utero) woman who initially had negative examinations. The patient was first evaluated at age 15 yr and was followed with Papanicolaou smears, pelvic examinations, and colposcopy every 6 mo for 2 yr prior to discovery of the malignancy. Palpation aided by colposcopy allowed direct biopsy of the small asymptomatic lesion on the right posterolateral wall of the upper third of the vagina. Changes consistent with adenosis were observed in the upper anterior and posterior vaginal walls, but a transition from benign adenosis to adenocarcinoma was not demonstrated. The individual at high risk of development of adenocarcinoma is under the age of 24 yr and has symptoms of abnormal bleeding or discharge, or extensive columnar ectopy of the cervix or vagina. Frequent Papanicolaou vaginal smears and regular, careful palpation with biopsy of all suspicious cystic or nodular vaginal masses are minimum requirements for screening such patients. Colposcopy has also proved useful. (10 refs)

79-2091 Ultrastructure of Clear Cell Adenocarcinoma of the Vagina and Cervix in DES-exposed Progeny: Analysis of 16 Cases (Meeting Abstract). (Eng) Dickerson, G. R. (Massachusetts General Hosp., Boston, MA); Welch, W. R.; Erlandson, R. A.; Robboy, S. J. *Lab Invest* 40(2): 252; 1979. (no refs)

79-2092 Diethylstilbestrol-induced Upper Genital Tract Abnormalities. (Eng) Haney, A. F. (Div. Reproductive Endocrinology and Oncology, Duke Univ. Medical Center, Durham, NC, 27710); Hammond, C. B.; Soules, M. R.; Creasman, W. T. *Fertil Steril* 31(2): 142-146; 1979.

Hysterosalpingography was used to quantitate upper genital tract changes among 13 women who had been exposed to diethylstilbestrol (DES) in utero, and the results were compared with those obtained from 22 non-DES-exposed nulliparous women. Among the DES-exposed patients, 40% had frequent complaints of primary dysmenorrhea and 47% complained of irregular menses. All but one had upper genital tract abnormalities. There were no significant differences between the upper genital tracts of patients with only cervical changes as opposed to those with both cervical and vaginal changes. The upper uterine segment, endometrial cavity area, and widest diameter of the endocervical canal were significantly smaller in the DES-exposed women than in the controls. Marked irregularity of the endometrial contour was apparent in virtually every patient. The circumference of the

endometrial cavity did not differ significantly between DES-exposed women and controls. The results support the hypothesis that DES may affect the developing hypothalamic-pituitary axis, thereby disturbing the normal cyclic release of gonadotropin. (11 refs)

79-2093 Evolution of Diethylstilbestrol-associated Lower Genital Tract Abnormalities (Meeting Abstract). (Eng) Antonioli, D. A. (Beth Israel Hosp., Boston, MA, 02215); Burke, L.; Rosen, S. *Lab Invest* 40(2): 238; 1979. (no refs)

79-2094 Vaginal Epithelial Changes in Young Women Enrolled in the National Cooperative Diethylstilbestrol Adenosis (DESAD) Project. (Eng) O'Brien, P. C. (Mayo Clinic Coordinating Center, Rochester, MN); Noller, K. L.; Robboy, S. J.; Barnes, A. B.; Kaufman, R. H.; Tilley, B. C.; Townsend, D. E. *Obstet Gynecol* 53(3): 300-308; 1979.

Clinical findings at the time of initial examination in 3,339 women enrolled in the National Cooperative Diethylstilbestrol (DES) Adenosis project are reported. Eighty-eight percent of the enrollees had documented prenatal exposure to DES. Vaginal epithelial changes (VEC), which were detected by colposcopy or iodine staining, occurred in 34% of 1,275 participants identified by review of prenatal records, 59% of the participants who requested entry into the project, and 65% of the participants who were referred by a physician. VEC were most commonly observed on the anterior and posterior vaginal walls, with extension into the lateral fornices usually occurring close to the cervix. Intraepithelial neoplasia and cancer were rare. Offspring with VEC were generally exposed in utero to larger total doses of DES over longer periods of time and beginning at an earlier age in gestation than were offspring without such changes. The occurrence of VEC was primarily associated with exposure initiated during the first 18 wk of gestation, and the frequency of VEC appeared to diminish with age over 26 yr. The single best predictor of VEC was the derived variable 'day started times dose.' (22 refs)

79-2095 Pathologic Findings in Young Women Enrolled in the National Cooperative Diethylstilbestrol Adenosis (DESAD) Project. (Eng) Robboy, S. J. (Harvard Medical Sch. and Massachusetts General Hosp., Boston, MA); Kaufman, R. H.; Prat, J.; Welch, W. R.; Gaffey, T.; Scully, R. E.; Richart, R.; Fenoglio, C. M.; Virata, R.; Tilley, B. C. *Obstet Gynecol* 53(3): 309-317; 1979.

Pathology findings in 3,246 biopsy specimens obtained during the initial examinations of 3,339 women enrolled in the National Cooperative Diethylstilbestrol (DES) Adenosis project are reported. Eighty-eight percent of the enrollees had

documented prenatal exposure to DES. Vaginal epithelial changes (VEC) on colposcopic examination or after iodine staining were observed in 34% of the 1,275 participants who were identified by review of prenatal records and in 53% of all participants. Forty-five percent of the participants with VEC who underwent biopsy had adenosis. Tuboendometrial epithelial cells were found in 3% of the cervical specimens positive for ectropion, 20% of the specimens with adenosis from the upper third of the vagina, 31% of those from the middle third, and 100% of those from the lower third. Metaplastic squamous epithelium was encountered in almost all biopsy specimens in which squamous epithelium was present. A usually mild inflammatory infiltrate was present in 66% of the specimens. Squamous cell dysplasia was rare and was found in only 0.4% of the participants identified through review of prenatal records. Four cases of clear cell adenocarcinoma, all in the upper third of the vagina, were found. Although three of these patients had had Papanicolaou smears suggestive of squamous cell dysplasia in the past, the clear cell adenocarcinoma in two of them was discovered as a result of the present examination. The results indicate that the frequency of adenosis reflects that of VEC. (29 refs)

79-2096 Blockade by Vitamin A of the Occurrence of Permanent Vaginal Changes in Mice Treated Neonatally with 5 α -Dihydrotestosterone. (Eng) Iguchi, T. (Shigei Medical Res. Inst., Yamada, Okayama 701-02, Japan); Takasugi, N. *Anat Embryol (Berl)* 155(2): 127-134; 1979.

The effect of vitamin A (VA: 200 IU/day sc for 5 days beginning on day 0 or 5 after birth, or 400 IU/day sc for 5 days beginning on day 15 after birth) on the induction of permanent vaginal changes by 5 α -dihydrotestosterone (DHT, 50 μ g/day sc for 5 days beginning on day 0 after birth) was studied using female C57Black/Tw mice. The mice were ovariectomized on day 10 or 80 after birth. Estrogen-dependent persistent proliferation and cornification of the vaginal epithelium and permanent proliferation and squamous metaplasia of the uterine epithelium occurred in the ovariectomized adult mice treated with DHT. VA given with, but not after, DHT prevented the occurrence of permanent vaginal and uterine changes. In 45% of the mice given DHT + VA, clear cells with pale cytoplasm appeared in the basal layer of the degenerating epithelium. These cells appeared in only 13% of the mice given DHT alone. The results suggest that VA may prevent permanent vaginal and uterine changes induced by DHT only when given in combination with the androgen in neonatal life. (23 refs)

79-2097 Myeloproliferative Disorder and Hepatocellular Adenoma Following Androgen Treatment of a Patient with Aplastic Anemia. (Jpn) Tsunematsu, Y. (Div. Pediatric Hematology-Oncology, Natl. Children's Hosp., Tokyo, Japan); Sasaki, M.; Koide, R.; Shimizu, K. *Jpn J Clin Hematol* 19(12): 1699-1707; 1978.

The case of a boy with aplastic anemia who subsequently developed a myeloproliferative disorder and hepatocellular adenoma following androgen treatment is reported. After diagnosis of the aplastic anemia at age 6, the patient was treated with androgenic steroids (stanazolol, oxymetholone, testosterone enanthate, and ethynandiol) for 5.5 yr before he developed severe anemia and a mass in the left upper abdominal quadrant. A liver scan showed hepatomegaly with a large filling defect. Hepatitis B surface antigen and α_1 -fetoprotein were not detected; bone marrow examination showed normoblastic hyperplasia with numerous ringed sideroblasts. Chromosome examination revealed aneuploidy in 50% of the analyzed cells (44,X-Y, -21/45XY, -21/46XY 1q+). He died suddenly at age 15. Autopsy showed a well-differentiated hepatocellular adenoma, hypercellular marrow with myeloid cells, but no increase of atypical cells. The hepatocellular adenoma was concluded to have been induced by the long-term use of androgenic steroids. (21 refs)

79-2098 The Influence of Prenatal or Neonatal Administration of 2-Bromo- α -ergocryptine on Pituitary Prolactin Secretion and Normal and Neoplastic Mammary Growth in Adult Mice. (Eng) Nagasawa, H. (Pharmacology Div., Natl. Cancer Res. Inst., Tokyo, Japan); Yanai, R. *J Endocrinol Invest* 1: 273-276; 1978.

The effects of pre- or neonatal exposure to 2-bromo- α -ergocryptine (CB-154: 0.3 mg sc during gestation days 12-15 or 0.6 mg sc during postnatal days 1-5) on pituitary prolactin secretion and mammary tumorigenesis were studied in a strain of SHN mice with a high natural incidence of mammary tumors. Pre- or neonatal treatment with CB-154 had no significant effects on the estrus cycle; mammary gland development; histologic structure of the ovaries; wts of the anterior pituitary, ovaries, or adrenals; or pituitary or plasma prolactin levels. The first mammary tumor appeared at 5 mo in the control group, at 6 mo in the group treated prenatally, and at 7 mo in the group treated postnatally. The cumulative incidence of mammary tumors increased in all groups with age, but the incidence was significantly lower in the CB-154-treated animals than in the controls at 8 mo. The results indicate that pre- or neonatal exposure to CB-154 has little adverse effects on the pituitary-ovary-mammary gland systems at advanced ages. (20 refs)

79-2099 Longterm Effects of Neonatal Treatment with Cortisol and/or Estrogen in the Female BALB/c Mouse (40396). (Eng) Ways, S. C. (Dept. Zoology, Cancer Res. Lab., Univ. California, Berkeley, CA, 94720); Bern, H. A. *Proc Soc Exp Biol Med* 160(1): 94-98; 1979.

The long-term morphologic effects of neonatal cortisol (C) treatment (50 μ g/day sc for postnatal days 1 through 10), with and without subsequent estrogen (E) treatment to (20 μ g/day 17 β -estradiol ip for days 11 through 15), on the re-

productive and immune systems of female BALB/c mice were studied. Abnormal cycling (persistent diestrus or prolonged estrus) was significantly more frequent among animals given C + E or E alone than among controls. C alone was not related to abnormal cycling. The estrous cycle was eliminated by ovariectomy at 5 mo of age. The mean body wt of mice treated with C + E was significantly lower than the control value at 60 days and 6 mo; C alone was associated with a significant decrease in body wt at 60 days. Thymus wts on day 180 were significantly increased in intact animals treated with C, and adrenal wts were significantly decreased by ovariectomy. The spleen inguinal lymph node, and adrenal wts of the intact treated animals were not significantly different from those of controls at 6 mo of age. The uteri of all animals were normal. Ovaries lacking corpora lutea and containing hypertrophied interstitial cells were found in 77% of the animals given C + E and in 81% of those given E alone. The spleen, thymus, inguinal lymph nodes, and adrenals had a normal histology. (23 refs)

79-2100 Endometrial Findings in Postmenopausal Women Receiving Long-Term Estrogen Therapy.

(Eng) Dabancens, A. (Casilla 6606-Correo 7, Santiago, Chile); Fuensalida, S.; Gonzalez, O.; Zanartu, J. *Cancer* 43(2): 658-660; 1979.

A prospective morphological study of the endometrium was undertaken in 43 postmenopausal women who had been given conjugated estrogens on a cyclic schedule for an av of 7 yr, 8 mo. Duration of therapy was positively correlated with the age of the patient. Ten of the women had received 0.625 mg of estrogen daily and 33 had received 1.25 mg/day; the incidence of withdrawal uterine bleeding was lower in the lower dose group. Hyperplastic lesions were more frequent and neoplastic conditions less frequent in the estrogen-treated patients compared with control subjects never treated with estrogen. The mean age of occurrence of these conditions was similar in treated patients and controls. Hyperplastic lesions were more frequent in patients given 1.25 mg/day estrogen than in those given only 0.625 mg/day, and the number of lesions increased with duration of treatment. Fifty percent of the treated women who had abnormal bleeding showed hyperplastic endometrial pathology. It is suggested that estrogen be given in the lowest possible dose for the shortest period of time to women without clinical and basal histologic evidence of endometrial disease. (16 refs)

Hosp., Worcester, MA, 01510); Chen, P. S.; Janower, M. L.; Farmelant, M. H.; Howard, J. T.; McDermott, W. *Am J Roentgenol* 132(3): 452-454; 1979.

The case of a patient in whom regression of a benign, oral contraceptive-associated, hepatic tumor was documented by angiographic and isotopic follow-up is presented. The patient became symptomatic following minor abdominal trauma. She had taken a mestranol-containing oral contraceptive for 5 yr. A 6-cm hepatic cell mass with marked hematoma formation was resected from the left lobe, but a very vascular 16-cm, nonhemorrhagic, hyperplastic nodule remained in the right lobe. One year later, angiography demonstrated marked reduction in the size of this tumor with some residual neovascularity. (12 refs)

79-2102 Mutagenicity of Complex Mixtures from Drinking Water. (Eng) Loper, J. C. (Dept. Microbiology, Univ. Cincinnati Coll. Medicine, Cincinnati, OH, 45267); Lang, D. R.; Smith, C. C. *Water Chlorination* 2: 433-450; 1978.

Residual organics concentrated from drinking water samples from five cities (Miami, Florida; New Orleans, Louisiana; Ottumwa, Iowa; Philadelphia, Pennsylvania; and Seattle, Washington) were tested for mutagenesis in the Salmonella/microsome system and for their ability to transform mouse BALB/3T3 1-13 cells. Each sample was processed sequentially to produce the reverse osmosis concentrate-organic extract (ROC-OE) and an ethanol-soluble eluate obtained from a macroreticular resin XAD-2 column (XAD eluate). Mutagenicity was detected for ROC-OE's from each city, the patterns being relatively stable for samples taken at 2- to 3-mo intervals. The ROC-OE's showed city-specific patterns regarding relative mutagenicities for *S. typhimurium* strains TA98 and TA100, relative amount of mutagenicity per milligram of residue, and distribution of mutagenic activity after fractionation. Metabolic activation produced little or no enhancement of mutagenic activity. ROC-OE fractions were 10- to 20-fold more toxic than the corresponding XAD eluates. Comparison of the transforming ability of a New Orleans ROC-OE with that of the known carcinogen 3-methylcholanthrene showed that the ROC-OE caused higher transformation rates at concentrations of 10-100 µg/ml. (12 refs)

79-2101 Contraceptive-associated Hepatic Tumor. (Eng) Benedict, K. T. (Dept. Radiology, St. Vincent

79-2103 Residue Organic Mixtures from Drinking Water Show In Vitro Mutagenic and Transforming

Activity. (Eng) Loper, J. C. (Dept. Microbiology, Coll. Medicine, Univ. Cincinnati, Cincinnati, OH, 45267); Lang, D. R.; Schoeny, R. S.; Richmond, B. B.; Gallagher, P. M.; Smith, C. C. *J Toxicol Environ Health* 4(5/6): 919-938; 1978.

Residual organic samples were concentrated from drinking water from representative US cities by reverse osmosis followed by liquid-liquid extraction and sorption-desorption on resin. City-specific patterns of dose-dependent bacterial mutagenesis and of bacterial toxicity were observed for these samples and for subfractions generated by sequential extractions. Mutagenicity was essentially independent of microsomal activation. One fraction of a New Orleans sample transformed BALB/3T3 cells in replicate experiments. (23 refs)

See also:

- *(Rev.): 79-1804, 79-1805, 79-1806, 79-1807, 79-1808, 79-1809, 79-1810, 79-1811, 79-1812, 79-1813, 79-1814, 79-1815, 79-1816, 79-1817, 79-1818, 79-1819, 79-1820, 79-1821, 79-1822, 79-1823, 79-1824, 79-1825, 79-1826, 79-1827, 79-1828, 79-1829, 79-1830, 79-1854, 79-1856, 79-1863, 79-1873, 79-1879, 79-1887, 79-1892, 79-1894.
- *(Phys.): 79-2108, 79-2113, 79-2119, 79-2120.
- *(Viral): 79-2131, 79-2135, 79-2150, 79-2202, 79-2257.
- *(Immun.): 79-2264, 79-2270, 79-2278, 79-2279.
- *(Path.): 79-2318, 79-2321, 79-2323.
- *(Epid.-Biom): 79-2331, 79-2332, 79-2333, 79-2334, 79-2335, 79-2336, 79-2337, 79-2338, 79-2339, 79-2340, 79-2344, 79-2351, 79-2360.

PHYSICAL CARCINOGENESIS

- 79-2104 Action of DTPA on Hepatic Plutonium. II. DTPA-induced Removal of Monomeric Plutonium from Mouse Liver Parenchymal Cells.** (Eng) Bhattacharyya, M. H. (Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL, 60439); Peterson, D. P.; Lindenbaum, A. *Radiat Res* 76(1): 180-186; 1978.

The mechanism by which diethylenetriaminepentaacetic acid (DTPA) chelation therapy induces plutonium excretion was studied in mouse liver parenchymal cells. The cells were isolated following the administration of DTPA (0.25 millimoles/kg iv) to female CF-1 mice previously inoculated iv with ^{239}Pu citrate (4.4 $\mu\text{Ci/kg}$). The isolated parenchymal cells contained 440 disintegrations/min (dpm) Pu/ 10^6 cells 24 hr after Pu injection, just prior to DTPA administration. The Pu content decreased to 330 dpm/ 10^6 cells at 6 hr and 140 dpm/ 10^6 cells at 24 hr following DTPA injection. These decreases were not seen in Pu-treated controls that did not receive DTPA. The net DTPA-induced decrease in Pu concentration in the parenchymal cell portion of the liver was calculated to be 21,300 dpm/g, which corresponded well with the net decrease in Pu concentration for the whole liver (21,600 dpm/g). Liver parenchymal cells isolated 6 hr following DTPA administration and containing 330 dpm Pu/ 10^6 cells were incubated in vitro in the absence of added DTPA. After 18 hr of incubation, the cells contained 130 dpm Pu/ 10^6 cells. This level corresponded to the level observed in cells isolated 24 hr after DTPA injection. Cells isolated from untreated mice lost only 15% of their Pu content during a similar in vitro incubation. These studies suggest that, in the liver, DTPA acts preferentially on the Pu associated with parenchymal cells. Isolated liver parenchymal cells appear to retain their ability to release Pu in vitro 6 hr after DTPA administration with no need for additional DTPA exposure. (9 refs)

- 79-2105 Adoptive Transfer of Immune Deficits of ^{90}Sr -treated Mice with Spleen Cells (Meeting Abstract).** (Eng) Levy, E. M. (Boston Univ. Medical Center, Boston, MA, 02118); Bennett, M.; Kumar, V.; Fitzgerald, P.; Cooperband, S. R. *Fed Proc* 38(3, part 2): 1279; 1979. (no refs)

- 79-2106 Chromosome Aberrations as a Biological Dose-Response Indicator of Radiation Exposure in Uranium Miners.** (Eng) Brandom, W. F. (Dept. Biological Sciences, Univ. Denver, Denver, CO, 80210); Sac-

comanno, G.; Archer, V. E.; Archer, P. G.; Bloom, A. D. *Radiat Res* 76(1): 159-171; 1978.

Cultured peripheral blood lymphocytes of 80 uranium miners and 20 controls matched for age and smoking habits were examined for the prevalence of structural chromosomal aberrations. A sputum-cell cytology study was also carried out in 64 of the miners. The latter study revealed that the proportion of lymphocytes with any chromosomal aberration as well as the proportion with two-hit aberrations were higher in miners with a greater percentage of atypical cells than in those with normal or mildly to moderately aberrant cells ($p < 0.02$), even though the radiation exposure was comparable for the two groups. Study of the culture lymphocytes revealed no significant difference between miners and controls in the prevalence of dicentric + rings. When either the proportion of miners with aberrant cells or the proportion of miners' cells containing aberrations was compared with similar proportions in the controls, all other aberration categories were significantly higher among the miners ($p < 0.001$). There was a marked decrease in the prevalence of deletions or dicentric + rings + deletions in miners exposed to the highest levels of radiation. Apart from the results in this group, all aberration categories except dicentric + rings demonstrated a significant and monotonic biological response that increased uniformly with estimated radiation dose. The aberration category that showed the most consistent pattern of increase with dose was pericentric inversions + translocations. The results demonstrate that the prevalence of dicentric + rings is not a good biological dose-response indicator. However, the prevalence of chromosome aberrations other than dicentric + rings is a sensitive biological indicator of low-level uranium miner irradiation. (42 refs)

- 79-2107 Effects of a Single High Dose of ^{55}Fe in Mice.** (Eng) Laissue, J. A. (Inst. Pathology, Kantonsspital, CH-6004 Lucerne, Switzerland); Burlington, H.; Cronkite, E. P.; Heldman, B.; Reincke, U. *Virchows Arch [Cell Pathol]* 29(4): 321-335; 1979.

The effects of a single high dose of iron-55 (2,800, 1,400, or 700 μCi iv) on 10- to 14-wk-old female C57BL/6J mice were investigated. A corresponding amount of cold iron was given to control animals by the same route. Mice given 2,800 μCi of radioiron died after a median survival time of 27 days with severe depletion of hematopoietic cells in bone marrow and spleen. They also displayed marked atrophy of lymphoid tissues and mild liver damage. After 1,400 or 700 μCi , median survivals were 117 and 439 days, respectively, compared with

847 days in controls. A dose-dependent pancytopenia was noted in the two lower dose groups. Nodular regenerative-type hematopoiesis was occasionally noted in the spleen. Atrophy of lymphoid tissues was moderate, and signs of liver damage were slight. The degree of organ hemosiderosis in experimental and control animals was slight to moderate. Tumors of hematopoietic and lymphoid tissues or osteosarcomas were seen in 12/14 radioiron-treated mice who survived > 300 days. Only three reticulum cell neoplasms, which are common in this mouse strain, were noted in control mice (679-977 days after treatment). Since the presence of radioactivity was the only difference between experimental and control mice, it is concluded that the induction of neoplasms must be linked to the radioactive decay of ^{55}Fe . (36 refs)

79-2108 Relevance of Specific Activity in Experimental Erythrocytocide by ^{55}Fe . (Eng) Reincke, U. (Medical Res. Center, Brookhaven Natl. Lab., Upton, NY, 11973); Brookoff, D.; Cronkite, E. P.; Hillman, M.; Wilcox, D.; Burlington, H. *Experientia* 35(2): 277-280; 1979.

The relevance of specific activity in experimental ^{55}Fe erythrocytocide was studied in Swiss albino mice who were inoculated iv with 5 μCi ^{55}Fe in 0.2-10 μg total iron. ^{55}Fe was used instead of ^{59}Fe in this model experiment designed to illustrate and define the degree of competition between radioactive and stable iron. The influence of concomitant iron load on isotope uptake was plainly visible. Relative organ uptake increased as a function of iron load in the liver and kidneys but it decreased in the bone marrow and blood. With the passage of time, the remaining isotope in each organ converged toward a common value regardless of initial iron load. This occurred at different speeds in different tissues and required 7 wk in the blood, 9 wk in the hindlegs, and > 10 wk in the liver and kidneys. Whole body iron retention was not influenced by the injected iron load. Thus, the observed organ-specific differences were due to differences in initial iron distribution and not to differences in iron elimination via the kidney and intestines. The data reemphasize the relevance of specific activity for the organ distribution of injected radioiron. Most likely, competition between radioactive and stable iron at the transferrin binding site and at the site of the erythron determines the initial isotope uptake in bone marrow and blood. The present results show that ionic iron can be given iv in amounts far exceeding the free-iron-binding capacity of serum. Therefore, the relevance of specific activity does not so much concern the feasibility as it does the reproducibility of ^{55}Fe erythrocytocide. (17 refs)

79-2109 Mutagenesis in Yeast Cells by Storage in Tritiated Water. (Eng) Ito, T. (Inst. Physics, Coll. General Education, Univ. Tokyo, Meguroku Komaba 3-8-1, Tokyo 153, Japan); Kobayashi, K. *Radiat Res* 76(1): 139-144; 1978.

The mutagenic effects of tritiated water on *Saccharomyces cerevisiae* cells in suspension were studied by measuring mitotic gene conversion at *trp 5*. At both 31 and 62 mCi/ml $^3\text{H}_2\text{O}$, the frequency of revertants increased linearly with the time that the cells remained in suspension with $^3\text{H}_2\text{O}$. The frequency increase per unit treatment time indicated a significant dependence upon $^3\text{H}_2\text{O}$ concentration. Based on the calculated β -particle dose, the mutagenicity of $^3\text{H}_2\text{O}$ was two or three times higher than that produced by γ irradiation with ^{137}Cs . (10 refs)

79-2110 Acute Monocytic Leukemia in an Irradiated Beagle. (Eng) Tolle, D. V. (Div. Biological and Medical Res., Argonne Natl. Lab., 9700 S. Cass Ave., Argonne, IL, 60439); Seed, T. M.; Fritz, T. E.; Lombard, L. S.; Poole, C. M.; Norris, W. P. *Vet Pathol* 16(2): 243-254; 1979.

Acute monocytic leukemia was induced by chronic irradiation in a female Beagle dog, and the subsequent clinical course, hematology, necropsy findings, histological findings, and leukemic cell characteristics are described. The dog had received a total of 2,000 R of protracted whole-body γ -radiation from ^{60}Co over a 117-day period, beginning at the age of 14 mo. Three years following the termination of radiation exposure, the animal developed hematologic changes consistent with a myeloproliferative disorder. Peripheral blood and bone marrow findings during the 7-mo period before death showed progressive anemia with increased numbers of platelets, immature granulocytes, monocytes, and promonocytes. A period of partial remission occurred that lasted from days 113 to 59 before death. During this time the peripheral blood was aleukemic, although there was marked thrombocytosis and abnormal erythropoiesis that was evidenced by bizarre circulating nucleated RBC, anisocytosis, poikilocytosis, and Howell-Jolly bodies. The dog had a terminal crisis with marked leukocytosis; most of the peripheral blood cells were bizarre monocytes and promonocytes. At necropsy, diffuse and focal infiltration of the spleen, liver, lymph nodes, heart, kidney, and gastrointestinal wall with immature neoplastic cells resembling monocytes and monocytic precursors was observed. The monocytic differentiation of the invasive cell population was confirmed by morphological, cytochemical, histological, ultrastructural, and in vitro cell culture studies. (22 refs)

79-2111 Radiation-induced Chromosome Aberrations in Nuclear-Dockyard Workers. (Eng) Evans, H. J. (Medical Res. Council, Clinical and Population Cytogenetics Unit, Western General Hosp., Edinburgh, Scotland); Buckton, K. E.; Hamilton, G. E.; Carothers, A. *Nature* 277(5697): 531-534; 1979.

The incidence of chromosome aberrations in the peripheral blood lymphocytes of 197 dockyard workers was followed over a 10-yr period from 1968 to 1978. These workers were

exposed to mixed neutron- γ radiation during the refueling of nuclear reactors, but most exposures were below the internationally accepted max permissible level of 5 rem(roentgen-equivalent-man)/yr. The data showed a significant dose-dependent increase in chromosome aberrations in the peripheral blood WBC of the workers. There were no detectable second-order effects of dose, and all data were consistent with a linear dose response. Susceptibility to radiation-induced chromosome damage increased statistically with age, the trend being significant for dicentric aberrations. For all types of damage, the dependence on "recent" dose was greater than that on "early" dose, but the trend was not significant. There was no apparent increase in deaths attributed to or associated with leukemia in the area that included the dockyard during the period 1967 to 1977. (24 refs)

- 79-2112 Metastatic Cancer in Guinea Pigs Irradiated with Grenz Rays.** (Eng) Wulf, H. C. (Dept. Dermatology, Finsen Inst., 49 Strandboulevarden, DK-2100, Copenhagen O, Denmark); Hou-Jensen, K. *Arch Dermatol* 115(2): 176-178; 1979.

Four of 11 guinea pigs irradiated with 100, 200, or 300 rads of grenz rays (ie, long wavelength x-rays) four times weekly for 2 yr and observed for an additional 3 yr developed squamous cell carcinomas of the skin. All carcinomas occurred in animals that had received one of the two higher radiation doses. Three affected animals had regional lymph node metastases. Neoplastic cells showed the same degree of differentiation in the primary tumors as in the lymph nodes. (11 refs)

- 79-2113 Low-Level X-Radiation-induced Vascular Alterations in Normal and DMBA-treated, Tumor-bearing Cheek Pouch Epithelium of Syrian Hamsters.** (Eng) Lurie, A. G. (Univ. Connecticut Health Center, Farmington, CT, 06032); Rippey, R. M. *Radiat Res* 76(1): 127-138; 1978.

A study was made of late changes in vascular volume and perfusion of normal and tumor-bearing Syrian hamster cheek pouch epithelium initially treated with 7,12-dimethylbenz-(a)anthracene (DMBA) and/or repeated low-level x-radiation. The hamsters received a single 20-R head and neck irradiation per week for 17 wk. During weeks 1-5 and 7-11, 0.1% DMBA was applied topically to the right cheek pouches 2x/wk (24 hr before and after irradiation). All animals were sacrificed 39 wk after the first treatment. Functional hemodynamic studies were followed by histopathologic evaluations of all tissues. Hamsters treated with radiation only had no tumors, whereas 53% of the DMBA-treated animals had tumors and 75% of the animals treated with DMBA + radiation had tumors. Most of the excess tumor-bearing animals had extremely dysplastic papillomas that were considered to be premalignant lesions that eventu-

ally become invasive carcinomas. Irradiated cheek pouches had increased blood volume, and DMBA-treated tumor-bearing pouches had increased blood volume and perfusion. DMBA + radiation-treated tumor-bearing pouches had increased blood volume similar to that seen in irradiated pouches and increased blood perfusion similar to that seen in DMBA-treated, tumor-bearing pouches. Although the presence of DMBA-induced tumors was related to changes in vascular perfusion in all groups, low-level x-radiation appeared to alter changes in blood volume caused by DMBA or DMBA-induced tumors. (34 refs)

- 79-2114 Radiation-induced Cancer of the Esophagus after Postoperative Irradiation for Breast Cancer.** (Jpn) Ito, I. (Dept. Radiology, Gunma Univ. Sch. Medicine, Maebashi, Japan); Miyaishi, K.; Mitsuhashi, N.; Ito, J.; Inoue, T.; Niibe, H. *Nippon Acta Radiol* 38(10): 985-991; 1978.

Two cases of radiation-induced esophageal cancer after postoperative irradiation for breast cancer are reported. The latent periods were 12 and 16 yr and the radiation doses were 4,180 and 1,860 rads, respectively. The breast cancers were papillotubular carcinomas, and the esophageal cancers were a poorly differentiated and a moderately differentiated squamous cell carcinoma. Both esophageal lesions were serrated. (24 refs)

- 79-2115 Postirradiation Mixed Mullerian Tumors of the Uterus: A Comparative Clinicopathological Study (Meeting Abstract).** (Eng) Varela-Duran, J. (Dept. Pathology, Univ. Minnesota Medical Sch., Minneapolis, MN, 55455); Nochomovitz, E.; Dehner, L. P. *Lab Invest* 40(2): 290-291; 1979. (1 ref)

- 79-2116 Postirradiation Sarcoma of Bone: A Perspective.** (Eng) Tountas, A. A. (Dept. Pathology, Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario, Canada M4X 1K9); Fornasier, V. L.; Harwood, A. R.; Leung, P. M. *Cancer* 43(1): 182-187; 1979.

The literature on postirradiation sarcoma of bone is reviewed, and 10 cases that were seen in a 20-yr period at one hospital are reported. In each of the 10 cases, the postirradiation sarcoma arose in previously healthy bone that had been included in the radiation field. Histologically, 6 were osteosarcomas, 1 was a chondrosarcoma, 2 were fibrosarcomas, and 1 was a sarcoma that was completely undifferentiated. The postirradiation sarcomas were particularly aggressive, with most of the patients having extensive metastases. By the time of diagnosis, none of the 10 cases was amenable to curative surgical resection. The overall incidence was calculated as 0.035% of all irradiated 5-yr survivors. When these data were combined with those of three other large series presented in

the literature, a dose-incidence curve could be deduced. On the basis of the human and animal data reviewed, it is concluded that the risk of radiation-induced sarcoma (0.05%-0.2%) is so low in the dose range of modern radiotherapeutic practice (4,000-7,000 rads) that it does not represent a contra-indication to the use of radiation therapy. (40 refs)

- 79-2117 An Atomic Bomb Survivor with Multiple Myeloma Accompanied by Basal Cell Carcinoma and Rectal Adenocarcinoma.** (Jpn) Yamaguchi, H. (Dept. Internal Medicine, Japanese Red Cross Society, Nagasaki Atomic Bomb Hosp., Nagasaki, Japan); Uchiyama, E.; Toyota, S.; Sugihara, H.; Takahara, O. *Jpn J Clin Hematol* 19(11): 1545-1550; 1978.

The case report of a Japanese atomic bomb survivor with multiple myeloma (IgG, heavy chain-type), basal cell carcinoma, and rectal adenocarcinoma is presented. The patient, a 46-yr-old woman, was 2 km from the epicenter at the time of the blast; therefore, the radiation level to which she was exposed was too low to cause the myeloma. Immunological studies revealed that she had a lowered cell-mediated immunity: negative purified protein derivative of tuberculin reaction, 37.5% T-cell lymphocyte level, and 45% lymphocytic transformation with phytohemagglutinin. Prednisolone (PN: 40 mg/day) and melphalan (2 mg/day) were administered daily until a basal carcinoma was discovered 9 mo later. After resection of this tumor, the dose of PN was lowered to 5-10 mg/day. The total duration of chemotherapy was 77 wk. Ten months later, the patient was found to have a rectal adenocarcinoma. Suppression of the immunological surveillance system associated with the myeloma is thought to be the cause of the multiple tumors in this patient. (13 refs)

- 79-2118 Solar Cycles and Malignant Melanoma.** (Eng) Viola, M. V. (Dept. Medicine, Univ. Connecticut Health Center, Farmington, CT, 06032); Houghton, A.; Munster, E. W. *Med Hypotheses* 5(1): 153-160; 1979.

A hypothesis is offered to explain the recent observation that the incidence of melanoma in Connecticut increases following max sunspot activity. It is proposed that sunspot cycles modulate the amount of stratospheric ozone and thus, indirectly, the amount of UV-B (290-320 nanometers) flux at the earth's surface. In both animal test systems and in human epidemiological studies, UV-B has been implicated as the major cause of skin cancer, including melanoma. A peak of sunspot activity occurred in 1957. According to data from the Connecticut Tumor Registry, there was a 22.2% increase in 1959 and a 10.5% increase in 1960 in incidence rates of melanoma above that anticipated by a linear regression equation relating melanoma incidence to time. Ozone variation was only 1%-2% decreased preceding this incidence rise. The increase in melanoma incidence related to a given reduction

in ozone depletion in this hypothesis is in great excess of that predicted by existing models relating anthropogenic ozone depletion and skin cancer. (27 refs)

- 79-2119 Bowen's Disease and Squamous Cell Carcinoma. Occurrence in a Patient with Psoriasis after Topical, Systemic, and PUVA Therapy.** (Eng) Tam, D. W. (Skin and Cancer Hosp., 3322 N. Broad St., Philadelphia, PA, 19140); Van Scott, E. J.; Urbach, F. *Arch Dermatol* 115(2): 203-204; 1979.

Multiple lesions of Bowen's disease and squamous cell carcinoma developed on the penis and pubic areas of a dark-complexioned, circumcised, 32-yr-old man with psoriasis who was undergoing treatment with psoralen and long-wave UV radiation (PUVA). A cumulative dose of >3,700 joules/cm² of UV radiation had been administered over a 3-yr period, a dose higher than that received by most PUVA patients. The cancerous lesions erupted precipitously in sites not normally prone to skin cancer. There was no known exposure to arsenic or ionizing radiation to the genitalia. In light of the possible association of cutaneous neoplasia with PUVA in this case, it seems advisable to use PUVA therapy as conservatively as possible in highly selected patients and that such patients be monitored closely after treatment. (6 refs)

- 79-2120 Development of Acute Myeloid Leukaemia in a Patient with Psoriasis Treated with Oral 8-Methoxypsoralen and Longwave Ultraviolet Light.** (Eng) Hansen, N. E. (Section Haematology, Dept. Medicine, Hvidovre Hosp., Kettegards Alle, DK-2650 Hvidovre, Denmark). *Scand J Haematol* 22(1): 57-60; 1979.

The development of acute myeloid leukemia in a 68-yr-old woman treated with 8-methoxypsoralen and long-wave UV light (PUVA) for psoriasis is reported. The PUVA treatment was administered for 11 mo, and it was terminated 2 yr before the patient was hospitalized with leukemia. When activated by UV light, 8-methoxypsoralen reacts with pyrimidine bases in opposite strands of the DNA duplex, thus cross-linking the DNA molecule. There is substantial evidence that PUVA induces profound changes on the molecular, chromosomal, and cellular levels and that it may induce cancer. It is quite possible that PUVA may induce changes in the hematopoietic system. Since the present case is the second reported occurrence of hematological disease in a PUVA-treated patient, a close and comprehensive follow-up of PUVA-treated patients is warranted. (16 refs)

- 79-2121 Toxicological Assessment of Potential Hazards from New Inorganic Fibers.** (Eng) Pigott, G. H. (Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Nr Macclesfield, Cheshire SK10 4TJ, En-

gland); Ishmael, J. *J Soc Occup Med* 29(1): 20-21; 1979.

An experimental program for evaluating the potential health hazards associated with inorganic fibers is discussed. To assess the hazards associated with a new fiber, lesions identical or very similar to those in humans are produced in rats. The potential hazard from inhalation of fibers is dependent on particle size, as only fibers with diameters less than 3-3.5 μm are respirable. A macrophage cytotoxicity test followed by ip or intratracheal injections of fiber suspensions into rats are used to test for fibrogenic potential. A severe test for potential mesothelioma production involves the single intrapleural injection of a large amount (20 mg) of fiber. This test, which is sensitive and gives clear cut results, showed no potential for mesothelioma production associated with alumina fiber, but a 15% rate of mesothelioma production with chrysotile asbestos. Both fibrosis and carcinogenesis can be assessed by inhalation experiments. The hazards of fiber ingestion are assessed by long-term feeding studies for chronic toxicity and carcinogenicity. (4 refs)

79-2122 The Induction of Rat Splenic Lymphocyte Blastogenesis by Alveolar Macrophages Following Chronic Asbestos Inhalation (Meeting Abstract). (Eng) Kagan, E. (Georgetown Univ. Medical Center, Washington, DC, 20007); Miller, K. *Fed Proc* 38(3, part 2): 1204; 1979. (no refs)

79-2123 Surface Charge in Foreign Body Carcinogenesis. (Eng) Andrews, E. J. (ETHICON Res. Foundation, Somerville, NJ, 08876); Todd, P. W.; Kukulinsky, N. E. *J Biomed Mater Res* 13(2): 173-187; 1979.

The importance of surface charge in foreign body carcinogenesis was evaluated by implanting bipolar polystyrene thermoelectrets formed in variously charged electrical fields (500-3,125 volts/cm) into male C3H/HeJ mice. Mice implanted with charged electrets had tumor rates similar to those in control groups. The combined data for mice with charged implants showed a tumor rate of 26.9%, compared with 17% for mice bearing electrets that were not exposed to an electric field (V-0 group) and 6% for mice bearing electrets that were exposed to 3,125 volts/cm (V-3125 group) and then rubbed with sterile sandpaper until no smooth surface remained. These data, however, were not statistically significant. Differences in tumor rates among the charged electret groups were minor except for the V-2000 group, which had a rate of 15.79%, lower than the V-0 control. These results suggest that neither the presence nor the intensity of the charge had any effect on tumorigenesis. The cumulative probabilities of tumor development as a function of time were calculated by actuarial techniques. The combined electret group had a higher probability, culminating at 0.58 at 133 wk when the study was terminated. The highest probability achieved by the V-0 control group was 0.17 at 117

wk. Although statistically significant differences in tumor rates could not be demonstrated at the 5% level, a definite trend toward increased tumor incidence existed in mice having charged electrets. The latent period of tumor induction varied little between groups and averaged approx 700 days. No conclusions regarding the tumorigenic effect of electropositive vs electronegative sides of the electret were made, although most tumors arose on the electronegative (body) side of the electrets. An occasional tumor (2/25) arose on both sides of a single electret. The antigenicities of tumors tested by excise and challenge techniques were weak. The immunologic relationship between top- and bottom-growing tumors on a single electret could not be determined adequately because of the weak antigenicity. (55 refs)

79-2124 Biologic Determinants of Tumor Growth in Healing Wounds. (Eng) Pendergrast, W. J. (Dept. Surgery, Emory Univ. Sch. Medicine, Atlanta, GA); Futrell, J. W. *Ann Surg* 189(2): 181-188; 1979.

The growth of an id transplanted methylcholanthrene (MCA)-induced liposarcoma (MCA-2) in surgical scars and healing operative wounds was studied in adult female Sewall-Wright strain-2 guinea pigs. Inoculation of tumor cells into 3-, 9-, or 11-wk-old scars resulted in tumor incidences of 78%, 50%, and 85%, respectively, whereas inoculation into acute wounds resulted in only a 20% tumor incidence. The tumor growth rate was also enhanced by inoculation of tumor cells into scar tissue. When wounds were made 1 wk after MCA-2 inoculation, the latency period between tumor injection and the appearance of palpable tumor was not decreased, but the subsequent rate of tumor growth around the wounds was significantly greater than the tumor growth rate in unwounded control animals. The results support the hypothesis that the relative paucity of lymphatic channel regeneration within scar tissue can render it a potential "immunologically privileged site," such that early recognition and destruction of tumor cells within the scar may be delayed long enough for the tumor to grow to a "critical size." (16 refs)

See also:

*(Rev.): 79-1831, 79-1832, 79-1833, 79-1834, 79-1874, 79-1879, 79-1882.

*(Chem.): 79-1898, 79-1899, 79-1945, 79-2029.

*(Viral): 79-2207, 79-2257.

*(Immun.): 79-2268.

*(Epid.-Biom.): 79-2331, 79-2341, 79-2342, 79-2343, 79-2354.

VIRAL CARCINOGENESIS

79-2125 Persistence of Avian Oncoviruses in Chicken Macrophages. (Eng) Gazzolo, L. (Unite de Virologie, Place Joseph Renaut, 69008 Lyon, France); Moscovici, C.; Moscovici, M. G. *Infect Immun* 23(2): 294-297; 1979.

The presence of avian oncoviruses in plasma and macrophages (MP) from chickens infected with sarcoma or leukosis viruses was examined. In chickens infected with two avian leukosis viruses, myeloblastosis-associated virus (MAV-2) or Carr Zilber-associated virus (CZAV), infectious virus was found only in MP obtained from the peripheral blood 6-31 mo after viral infection. Neutralizing antibodies were always present in the sera of all chickens. In chickens infected with the Prague strain of Rous sarcoma virus subgroup A (PR-RSV-A) or avian sarcoma virus B77, no virus was detected in plasma or MP obtained 2-24 mo after infection either from chickens bearing a tumor or from chickens after tumor regression. The search for virus was also negative in cocultivation experiments using mixed cultures of MP and fibroblasts. Neutralizing antibodies were not detected in the sera obtained from birds infected with PR-RSV-A. MAV-2 was detected in spleen and bursa cells as well as in MP 1 mo after injection, but the percentage of MAV-2-positive spleen or bursa cells was 100- to 400-fold lower than that of MAV-2-positive MP. No sarcoma virus was detected in cells or in the plasma, confirming the previous results. The persistence of avian leukosis viruses in MP may be of significance when it is related to the long latent period preceeding the expression of oncogenic disease in animals inoculated with these viruses. (17 refs)

79-2126 Reverse Transcriptase from Avian Myeloblastosis Virus. (Eng) Houts, G. E. (Life Sciences, Inc., St. Petersburg, FL, 33707); Miyagi, M.; Ellis, C.; Beard, D.; Beard, J. W. *J Virol* 29(2): 517-522; 1979.

A comparatively simple, two-step chromatographic procedure that affords high yields of RNA-dependent DNA polymerase (RDDP, reverse transcriptase) from large amounts of avian myeloblastosis virus (AMV) is described. RDDP of >95% purity was obtained from 20- to 30-g lots of AMV by a two-step column chromatographic procedure employing diethylaminoethylcellulose and carboxymethylcellulose. Yields of RDDP varied from approx 20,000 to 35,000 units/g of virus. The specific activity of the enzyme was about 35,000-60,000 units/mg of protein. Free of detectable RNase activity, the product exhibited a mol wt of about 160,000 and an isoelectric point of 6.5, and it contained approx 2 moles of fatty acid per mole of enzyme. (22 refs)

79-2127 In Vitro Transformation of Hematopoietic Cells by Avian Erythroid and Myeloid Leukemia Viruses: A Model System for the Differentiation of Normal and Neoplastic Cells. (Eng) Graf, T. (Max-Planck-Institut fur Virusforschung, Biologisch-Medizinische Abteilung, D-7400 Tubingen, W. Germany); Beug, H.; Royer-Pokora, B.; Meyer-Glauner, W. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 625-639; 1978.

The in vitro transformation of hematopoietic cells by avian erythroid (AEV) and myeloid leukemia viruses (AMV and MC29) was studied. Chicken bone marrow cells infected with AEV, MC29, or AMV produced transformed foci as early as 3-4 days after infection. In their staining properties, the AEV- and AMV-transformed bone marrow cells resembled erythroblasts and myeloblasts, respectively, but the cells transformed by MC29 resembled macrophages. The erythroid markers Hb, histone H5, and chicken RBC surface antigen were detected in bone marrow cells transformed by AEV but not by MC29 or AMV. MC29-transformed bone marrow cells and, to a lesser extent, AMV-transformed cells were phagocytic. Both MC29- and AMV-transformed cells gave a specific fluorescence with serum prepared against cultured chicken macrophages and both possessed Fc receptors, whereas cells transformed by AEV were not phagocytic, did not stain with antimacrophage serum, and did not contain detectable Fc receptors. The target cells for AEV and the myeloid viruses could be separated. It is suggested that the target cells for MC29 and AMV belong to the myeloid lineage of differentiation and that the target cells for AEV belong to the erythroid lineage. AEV-transformed erythroblasts were inducible by butyric acid but not by dimethyl sulfoxide. These studies indicate that the erythroid and myeloid viruses do not affect a common population of stem cells, thus, that the differentiation stage of the target cells reflects the differentiation stage of the transformed cells. (17 refs)

79-2128 Tumor Specificity of Acute Avian Leukemia Viruses Reflected by Their Transformation Target Cell Specificity In Vitro. (Eng) Graf, T. (Biol.-Med. Abteilung, Max-Planck-Institut fur Virusforschung, D-7400 Tubingen, W. Germany); Royer-Pokora, B.; Meyer-Glauner, W.; Beug, H. *Med Microbiol Immunol (Berl)* 164(1/3): 139-153; 1977.

The results of current and previous studies concerning the tumor specificity of five transforming avian leukemia viruses are presented. These viruses included two erythroblastosis viruses [avian erythroblastosis virus (AEV) strain R and AEV strain ES] and three myeloid leukemia viruses [avian

myeloblastosis virus (AMV), avian myelocytomatosis virus strain MC29, and avian myelocytomatosis virus strain CMII]. Myeloid leukemia virus-transformed hematopoietic cells phagocytize fixed bacteria and latex beads, but AEV-transformed cells do not. Myeloid cells are dependent upon colony-stimulating factor for colony formation, but AEV cells are either weakly dependent or not dependent on this factor for colony formation. All three myeloid strains, but none of the erythroid strains, transform macrophage cultures, supporting the assumption that myeloid cells (macrophages) but not erythroid cells are the target cells for transformation by avian myeloid leukemia viruses. Both AEV strains are capable of transforming fibroblasts in vitro. Unlike AEV-transformed fibroblasts, MC29-transformed cells do not show an increased rate of deoxyglucose uptake. MC29-transformed chicken embryo fibroblasts and normal control cells possess similar amounts of large, external, transformation-sensitive (LETS) protein, but this protein is lost from AEV-transformed cells and Rous sarcoma virus-transformed cells. Although previous studies have demonstrated the sarcomagenicity of AEV-transformed fibroblasts, current attempts to induce solid tumors with MC29-transformed fibroblasts failed. The findings presented indicate that transforming avian leukemia viruses possess a high degree of in vitro target cell specificity in the hematopoietic system, reflecting the tumor spectrum obtained with the corresponding strains. (34 refs)

- 79-2129 Structural Analysis of the Avian Sarcoma Virus Transforming Protein: Sites of Phosphorylation.** (Eng) Collett, M. S. (Dept. Pathology, Univ. Colorado Medical Center, Denver, CO, 80262); Erikson, E.; Erikson, R. L. *J Virol* 29(2): 770-781; 1979.

The polypeptide product of the avian sarcoma virus (ASV) transforming (*src*) gene is a 60,000-dalton phosphoprotein designated pp60*src*. The sites of phosphorylation on the pp60 *src* molecule were characterized in an effort to understand the functional regulation in cells of the ASV transforming protein. The technique of limited proteolysis during reelectrophoresis showed that pp60*src* contains two major sites of phosphorylation, one involving phosphoserine and the other involving phosphothreonine, and possible additional minor sites of phosphorylation. By using N-formyl[³⁵S]methionyl-transfer RNA-f as a radiolabeled precursor in the cell-free synthesis of the *src* protein in conjunction with partial proteolysis mapping, the phosphoserine residue was found to be located on the amino-terminal two-thirds of the molecule, the phosphothreonine residue on the carboxy-terminal third. The phosphorylation of pp60*src* in cell extracts involved at least two protein kinases: the one that phosphorylated the major serine site was cyclic AMP-dependent and the other, acting on the threonine residue, was a cyclic nucleotide-independent phosphotransferase. Finally, analysis of the pp60*src* isolated from cells infected with a temperature-sensitive *src* gene mutant of ASV revealed that phosphorylation of the major threonine residue was severely reduced

when infected cells were grown at the nonpermissive temperature, whereas a phosphorylation pattern characteristic of wild-type pp60*src* was observed at the permissive temperature. As pp60*src* has an associated protein kinase activity, phosphorylation-dephosphorylation reactions may possibly be involved in the functional regulation of ASV-transforming-protein enzymatic activity. (20 refs)

- 79-2130 Description of Cell Populations Isolated In Vitro from LEW/CUB Rat Embryos.** (Eng) Vesely, P. (Inst. Molecular Genetics, Czechoslovak Acad. Sciences, Prague, Czechoslovakia); Kren, V.; Wyke, J.; Plaisner, V.; Sladka, M. *Folia Biol (Praha)* 24(6): 391; 1978.

The use of embryonic cells from highly inbred LEW/CUB rats for in vitro studies of neoplastic transformation by avian sarcoma viruses was investigated. Hepatocytes and epidermal cells were not cultured successfully, but no spontaneous transformation occurred in cultures of mixed embryo fibroblasts or kidney cells. The kidney cells were also negative for tumorigenicity in vivo, indicating the absence of an endogenous C-type virus in this strain or its resistance to induction. The genetic stability of LEW/CUB cells in vitro demonstrates that they are suitable for in vitro viral transformation studies. (1 ref)

- 79-2131 Effect of 5-Methylcytidine on Virus Production in Avian Sarcoma Virus-infected Chicken Embryo Cells.** (Eng) Guntaka, R. V. (Dept. Microbiology, Coll. Physicians and Surgeons, Columbia Univ., New York, NY, 10032); Katz, R. A.; Weiner, A. J.; Widman, M. M. *J Virol* 29(2): 475-482; 1979.

As part of a series of experiments designed to study the role of modified nucleosides in the transcription and processing of RNA, the effect of 5-methylcytidine (5mC), a minor constituent of RNA in procaryotes as well as eucaryotes, on virus production in avian sarcoma virus-infected chicken embryo fibroblasts was determined. Surprisingly, virus release into the medium was severely reduced in cultures treated with 5mC. In contrast to the effect of 5mC on virus release, intracellular levels of virus-specific RNA transcripts and protein levels were slightly elevated. Thus, substitution of methylcytidine monophosphate for cytidine monophosphate in viral RNA suppresses virus production while allowing normal levels of transcription and translation of viral RNA. Analysis of intracellular RNA transcripts on velocity gradients and virus-specific proteins in polyacrylamide gels did not reveal any qualitative differences between 5mC-treated and cytidine-treated cells. It is concluded that the effect of 5mC is probably at the level of virus maturation or packaging. (22 refs)

79-2132 *src* Gene Product from Different Strains of Avian Sarcoma Virus: Kinetics and Possible Mechanism of Heat Inactivation of Protein Kinase Activity from Cells Infected by Transformation-defective, Temperature-sensitive Mutant and Wild-Type Virus. (Eng) Rubsamen, H. (Institut für Virologie, Fachbereich Humanmedizin, Justus-Liebig-Universität Giessen, Frankfurter Strasse 107, 63 Giessen, W. Germany); Friis, R. R.; Bauer, H. *Proc Natl Acad Sci USA* 76(2): 967-971; 1979.

Sera from rabbits bearing Schmidt-Ruppin strain Rous sarcoma virus (RSV)-induced tumors precipitated a 60,000-dalton transformation-specific phosphoprotein (p60src) from chicken cells transformed by the homologous virus as well as by other strains [Prague strain RSV, Bryan high-titer strain RSV, and the Bratislava 77 strain of avian sarcoma virus (ASV)]. The mol wts ranged from 60,000 to 64,000. The p60src immunoprecipitated from cells transformed by each of these strains incorporated [γ - 32 P]ATP into the 53,000-dalton subunit of IgG, although with differing protein kinase activities. No protein kinase activity (ATP:protein phosphotransferase) was observed when immunoprecipitates from uninfected cells, untransformed cells infected by Rous-associated virus, or cells transformed by acute leukemia viruses, avian erythroblastosis virus, or myelocytoma virus 29 were used. The kinase reaction had a pH optimum at 5.9 and an apparent K_m for ATP of 4.9 μ M, and it was dependent on Mg^{2+} . Ca^{2+} could not be substituted for the latter. The kinase was cyclic AMP-independent. In order to test whether the protein kinase reaction is directly catalyzed by p60src, the in vitro temperature sensitivities of the kinase activities from cells infected by a transformation-defective, temperature-sensitive mutant and parental wild-type virus were compared. The first-order rate constant for inactivation of the kinase from extracts of cells infected by the mutant virus was two-fold greater than that from cells infected by wild-type virus. This result implicates protein kinase as an enzymatic activity of p60src. Concomitant with the loss of kinase activity by heat inactivation, p60src loses 60%-70% of its phosphate content. The kinetics of dephosphorylation parallel those for inactivation of the kinase activity, suggesting that the p60src kinase is itself dependent on phosphorylation for its activity. (19 refs)

79-2133 Alterations in Surface Proteins of Rat Cells Transformed by Avian Sarcoma Virus B77. (Eng) Chorvath, B. (Cancer Res. Inst., Slovak Acad. Sci., 880 32 Bratislava, Czechoslovakia); Duraj, J.; Hlubinova, K.; Valentova, N.; Simkovic, D. *Neoplasma* 25(5): 541-548; 1978.

The cell-surface proteins of uninfected rat embryo fibroblasts and cells transformed by the Bratislava 77 (B77) strain of avian sarcoma virus were analyzed by sodium dodecyl sulfate-acrylamide gel electrophoresis. Compared with the uninfected cells, the virus-infected cells showed: a slight decrease in the levels of two high-mol-wt proteins [one presumably corresponding to the LETS (large, external, transforma-

tion-sensitive protein)]; a decrease in a protein of approx 50,000 mol wt; increases in proteins with mol wts of approx 70,000-75,000 and 90,000-95,000; and a marked increase in a protein with a mol wt of 30,000-35,000. There were no major differences in the quantities of these proteins in two different virus-infected cell lines (LWF B77 and LWF B55) or between monolayer and spinner cell cultures. Metabolic labeling of the plasma membrane proteins confirmed the results obtained with electrophoresis, and metabolic labeling of the cell membrane proteins indicated that the proteins of mol wt 70,000-75,000 and 90,000-95,000 were glycoproteins. (19 refs)

79-2134 Change of Isozyme Pattern During Activation of a Transforming Gene Product. Its Relation to Other Biochemical Markers of Cellular Transformation and Differentiation. (Eng) Roth, S. L. (Univ. Pennsylvania Sch. Medicine, Philadelphia, PA, 19104); Kaji, A. *Biochim Biophys Acta* 583(2): 241-252; 1979.

Isozyme patterns of leucine aminotransferase (LAT) were studied in connection with glucose transport and DNA synthesis during the activation and deactivation of the transforming gene product in rat kidney cells transformed by a Rous sarcoma virus with a temperature-sensitive lesion in its transforming gene. On temperature shift-down of confluent transformed cells grown at 40 C in the presence of fresh serum, isozyme III of LAT appeared within 12-20 hr and increased from 24 to 48 hr. Upon temperature shift-up, isozyme I became the predominant form in 4 days, the major change occurring within the first 24 hr. Isozyme I was more characteristic of sparse cultures, whereas isozyme III was predominant in denser cultures. The rate of protein turnover was similar to the rate of loss of isozymes I and III during temperature shift-down and shift-up, respectively. The transformed cells were stimulated to synthesize DNA 8-12 hr after shift-down from 40 C. Once this induction of DNA synthesis had taken place, return of the cells to 40 C did not completely abolish the induced DNA synthesis for at least 16 hr. The LAT isozyme pattern reflected the state of differentiation of the cells, with isozyme I being more characteristic of the myotubes and isozyme III being more predominant in the undifferentiated cells. (31 refs)

79-2135 Effect of Hormones on the Activation and Accumulation of Oncornavirus in Cell Cultures. (Rus) Kuznetsov, O. K. (Lab. Biochemistry, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR); Gaber, V. K.; Lindenberg, T. Ia.; Kostetskaia, T. V.; Shmel'kova, V. I.; Bershtein, L. M.; Smida, Iu. *Vopr Onkol* 25(2): 42-44; 1979.

To evaluate the effects of various hormones on oncornavirus replication, chick embryo cells [group-specific (gs) antigen-negative] growing in monolayer were inoculated with Rous sarcoma virus (RSV) and 30 min later, exposed to medi-

um containing estradiol (1 $\mu\text{g/ml}$), testosterone (5 $\mu\text{g/ml}$), hydrocortisone acetate (10 or 40 $\mu\text{g/ml}$), thyroxine (3 $\mu\text{g/ml}$), or insulin (2 $\mu\text{g/ml}$). The presence of Gs antigen in the fibroblast cultures was assessed by complement fixation. Twelve chick embryo cell cultures were tested. Gs antigen was present in 3/12 cultures exposed to testosterone, 2/12 cultures exposed to estradiol, and in 1/12 cultures exposed to thyroxine. Inoculation of chickens with culture medium collected during the first 5 days of incubation with hormones did not result in tumor formation. (4 refs)

- 79-2136 **Monomer and Multimer Covalently Closed Circular Forms of Rous Sarcoma Virus DNA.** (Eng) Goubin, G. (Dept. Cellular Biology, Inst. Cancerology and Immunogenetics, Villejuif, France); Hill, M. *J Virol* 29(2): 799-804; 1979.

Monolayer cultures of chicken embryo fibroblasts were infected with the Schmidt-Ruppin strain of Rous sarcoma virus (RSV), subgroup D, or its temperature-defective derivative (*tsSR-D*), and the purified form I RSV DNA isolated 30 hr after infection was analyzed by neutral sucrose gradient sedimentation. The covalently closed circular molecules of viral DNA synthesized in the virus-infected cells were composed mainly of monomers sedimenting at 22S-27S. These monomers were detected by annealing with ^3H -labeled complementary DNA or by transfection assays. However, 11% of the infectious circles sedimented faster than the monomers. There was a peak at 32S that may correspond to dimer molecules. Traces of infectivity (about 3%) found between 32S and 65S suggest the presence of higher oligomers. In alkaline sucrose gradients, covalently closed monomers were found at 64S-71S. Transfection assays showed that the monomers were infectious, although alkali treatment reduced their infectivity to less than one-tenth of that found at neutral pH. Perhaps for this reason, no infectious dimers or higher oligomers were observed. Upon resedimentation, the 95S dimers could be separated from the monomers and detected by hybridization. (27 refs)

- 79-2137 **In Vitro, the Major Ribosome Binding Site on Rous Sarcoma Virus RNA Does Not Contain the Nucleotide Sequence Coding for the N-Terminal Amino Acids of the gag Gene Product.** (Eng) Darlix, J. L. (Departement de Biologie Moléculaire, Université de Genève, CH-1211 Geneva 4, Switzerland); Spahr, P. F.; Bromley, P. A.; Jatton, J. C. *J Virol* 29(2): 597-611; 1979.

Ribosome binding experiments with Rous sarcoma virus (RSV) RNA were performed with the use of a nuclease-treated reticulocyte lysate in order to determine directly whether the in vitro translation of the first gene (*gag*) is initiated within the same hundred nucleotides that are first reverse-transcribed in vitro. In addition, the length and the nucleotide sequence of the RSV RNA ribosome binding site were deter-

mined. Ribosomes from the reticulocyte lysate bound strongly and mainly to a region located in the 5' end of the RSV RNA molecule, between residues 9 and 53. This binding involved the participation of initiator transfer RNA and was sensitive to inhibitors of protein synthesis such as 7-methyl-guanosine monophosphate and aurintricarboxylic acid. The nucleotide sequence of this ribosome binding site contained a GUG codon centered at position 26 that was not in phase with any termination codon within the 5'-end nucleotide sequence of the RNA analyzed (101 residues). However, the predicted N-terminal amino acid sequence starting from this GUG codon (or even from any AUG or GUG codon in the 5' end of the RNA) did not coincide with that of the in vitro-synthesized product of the 5'-end proximal *gag* gene. Nevertheless, inhibition of ribosome binding to this site was accompanied by an inhibition of the in vitro translation of the *gag* gene. (36 refs)

- 79-2138 **Antigenic Determinants Specific to the Envelope Glycoprotein of Exogenous Avian Tumor Viruses.** (Eng) Marini, S. C. (Wistar Inst. Anatomy and Biology, Philadelphia, PA, 19104); Friis, R. R.; Halpern, M. S. *J Virol* 29(2): 805-807; 1979.

The immunogenicity of the envelope glycoprotein (VGP) of exogenous avian sarcoma virus (ASV) was assessed in 15B x 7₂ chickens positive (V+) for subgroup E endogenous Rous-associated virus (RAV-0). At 4 wk posthatch, several days after the collection of preinfection sera, eight of the V+ chickens were infected with the Prague strain of Rous sarcoma virus, subgroup A, and seven were infected with B₁₇ virus, subgroup C. Seven chickens were left uninfected. Serum samples were obtained 2 wk after infection and at 2-wk intervals thereafter. Antibody reactivity in the various sera to determinants of VGP was measured by indirect immunoprecipitation. As measured with viral test antigens of subgroups A, B, C, and D, increased levels of radioactivity, compared with preinfection levels, were detected in immune precipitates prepared with postinfection sera of infected V+ chickens. In tests of these sera against subgroup E VGP, a markedly reduced or negligible increase in precipitable radioactivity was detected relative to the increase measured with exogenous VGP. Little or no increase in precipitable radioactivity was measured with sera of uninfected V+ chickens. In virus neutralization assays, the sera of uninfected V+ chickens did not neutralize viruses of subgroups A-E. Postinfection sera of infected V+ chickens did not neutralize subgroup E virus and only neutralized exogenous virus of the same subgroup as that of the infecting virus. The immunoprecipitation and neutralization assays show that antibody in the sera of infected V+ chickens recognizes nonneutralizing determinants that, at least collectively, are present on the VGP of several, if not all, exogenous viruses. The absence of these determinants from the VGP of RAV-0 serves to distinguish them from group-specific determinants. These determinants, therefore, fall into a classification category in which cross-reactivity on non-group-specific determinants spans two or more subgroups. (9 refs)

79-2139 Nature of Rous Sarcoma Virus-specific RNA in Transformed and Revertant Field Vole Cells. (Eng) Krzyzek, R. A. (Dept. Microbiology, Univ. Minnesota Medical Sch., Minneapolis, MN, 55455); Lau, A. F.; Faras, A. J. *J Virol* 29(2): 507-516; 1979.

To determine the size classes of virus-specific RNA present in Rous sarcoma virus-transformed and revertant field vole cells, cytoplasmic and polyribosomal RNA's from these cells were fractionated by rate-zonal sedimentation and hybridized with a ³H-labeled complementary DNA viral probe. In contrast to Rous sarcoma virus-infected permissive avian cells, only two of three discrete species of virus-specific RNA were detected in the cytoplasm of these vole cells. They included genome-length 35S RNA and a 21S RNA. Viral 28S RNA, routinely detected in the cytoplasm of productively infected avian cells, could not be found. In addition, a low-mol-wt viral RNA sedimenting at < 16S was detected in both infected avian and vole cells. Because of its heterogeneity, this latter species is most likely generated from the intracellular degradation of the larger viral RNA's. The viral 35S and 21S RNA's were found to be associated with the total polyribosomes from these vole cells. Studies were also performed to determine the distribution of total viral genomic and sarcoma-specific RNA sequences among the size classes of fractionated total polyribosomes. In both transformed and revertant vole cells, most of the cytoplasmic viral RNA sequences were also associated with all size classes of the total polyribosomes, and the two cell types distributed similarly. Sarcoma-specific sequences were present on both the 35S and 21S RNA species. These data suggest that the expression of the viral transforming gene in revertant field vole cells may be controlled at some stage subsequent to translation of the viral RNA. (32 refs)

79-2140 Phenotypes of Rous Sarcoma Virus-transformed Fibroblasts: An Argument for a Multifunctional Src Gene Product. (Eng) Friis, R. R. (Justus-Liebig-Universität, Institut für Virologie, Frankfurter Strasse 107, D-6300 Giessen, W. Germany); Schwarz, R. T.; Schmidt, M. F. *Med Microbiol Immunol (Berl)* 164(1/3): 155-165; 1977.

Speculations concerning the nature and function of the *src* gene product of Rous sarcoma virus are made on the basis of studies of the phenotypes of transformed cells. It is believed that the phenotypic differences reproducibly observed in cell cultures infected with different transformation-defective mutants must be derived from mutations in the *src* gene and consequent changes in its function. These functional changes may be quantitative or qualitative. There is an analogy between *src* and *pol*, the genetic unit coding for reverse transcriptase. Of all mutants in RNA tumor virus replication or transformation, the majority have been transformation defective; thus, they are presumably defective in *src*. Of the remainder, 90% have been defective in *Pol*. Multifunctional proteins may respond at higher probability to each mutation because

a high precision of protein conformation is required, although this hypothesis has not been proved. Changes in the function of the *src* gene product may be qualitative rather than quantitative, as some mutants grow logarithmically at 42 C without exhibiting a transformation-specific increase in hexose transport. In the presence of tunicamycin, the same mutants show increased hexose transport when shifted to the permissive temperature (35 C). Since this compound affects glycosylation, the *src* gene product must be independent of this reaction. (21 refs)

79-2141 Neural Crest Cells: Temperature-dependent Transformation by Rous Sarcoma Virus. (Eng) Greenberg, J. H. (Lab. Developmental Biology and Anomalies, Natl. Inst. Dental Res., NIH, Bethesda, MD, 20014); Bader, J. P. *Cell Differ* 8(1): 19-27; 1979.

The effects of infecting cultured neural crest cells from chick embryos with a mutant (RSV-BH-Ta) of the Bryan high-titer strain of Rous sarcoma virus (RSV) before or after their morphological differentiation into pigmented cells were studied. Uninfected cells proliferated slowly. Infection with the mutant before differentiation (culture day 2) at either the permissive (37 C) or the nonpermissive temperature (41 C) dramatically stimulated cell proliferation, although at 41 C growth appeared to stop after several weeks. At the permissive temperature, the neural crest cells acquired extensive vacuoles and were greatly enlarged in comparison with uninfected cells or infected cells grown at 41 C. These characteristics are similar to those of fibroblasts (FB) transformed with RSV-BH-Ta at 37 C. At the nonpermissive temperature, infected cells were not vacuolated and differed slightly in appearance from that of uninfected cells. However, even at confluency they did not show the characteristic morphology of untransformed FB or RSV-BH-Ta-infected FB at 41 C. Infection at either temperature prevented the neural crest cells from differentiating morphologically into pigmented cells or into any other derivatives previously observed in culture. Infection of the cells after they had differentiated into pigment cells induced rapid cell proliferation at both temperatures. In addition, these cells lost their pigment granules and, after 1-2 wk, were morphologically indistinguishable from those infected before they had differentiated. The results of infection of neural crest cells with a virus that induces a temperature-dependent transformation demonstrate that even at the nonpermissive temperature, the virus has an effect on cell growth and morphology and it may be actively involved in regulating the state of differentiation of certain types of cells. (20 refs)

79-2142 In Vitro and In Vivo Properties of Neoplastic LEW/CUB Cells. (Eng) Vesely, P. (Inst. Molecular Genetics, Czechoslovak Acad. Sciences, Prague, Czechoslovakia); Kren, V.; Wyke, J.; Jirasek, A.; Elleder, M.; Bannikov, G. *Folia Biol (Praha)* 24(6): 392-394; 1978.

LEW/CUB rat cells transformed by the avian sarcoma viruses (ASV), SR-RSV-D, B77, and LA334 (a temperature-sensitive mutant of B77) were studied with respect to malignancy in vivo and behavior in vitro. Mixed embryo fibroblasts (F cells), male embryo liver cells (L cells), male embryo kidney cells (K cells) and their two clones (A, G cells) were transformed and the following characteristics established: pattern of virus rescue, efficiency of plating on a solid substratum and in soft agar, tumorigenicity in syngeneic rats, population doubling time, and behavior in vitro. Almost all the transformed clones yielded pleiomorphic sarcomas when injected sc (10^6 cells) into adult syngeneic LEW/CUB rats. The tumorigenic cells generally manifested the transformed morphotype and anchorage independence, with the exception of F cells infected with B77 or SR-RSV-D, kidney cells infected with B77 and A cells infected with LA334. These cells did not grow in soft agar. With one exception (G cells infected with B77) all the virogenic cells were tumorigenic. All the tumors appearing after injection of LEW/CUB cells transformed by ASV in vitro were noninvasive, which correlated with their behavior in vitro. (3 refs)

- 79-2143 New Endogenous RNA Tumor Viruses.** (Eng) Chen, Y. C. (Dept. Biological Sciences and Genetics Center, North Texas State Univ., Denton, TX, 76203). *Tex J Science* 30(5, Suppl): 3-12; 1978.

New endogenous RNA tumor viruses obtained from cells of members of the avian family, Phasianidae, were studied. Helper activity for the defective Bryan high-titer strain of Rous sarcoma virus (RSV) was found in normal embryo fibroblast cultures of Ghighi, Green, Silver, Mongolian, and Swinhoe pheasants, Chinese quail, and Chukar (Stone partridge). All but one of the new pseudotypes failed to produce foci in mammalian cell cultures; Chinese quail virus induced foci on European field vole and mouse cells with high efficiency. The polycation, Polybrene, enhanced foci formation on chicken cells infected with the new RSV pseudotypes. The viruses from Mongolian and Swinhoe pheasant, Chinese quail, and Chukar cells specified unique envelope determinants, and a leukosis helper virus, capable of inducing specific homologous pseudotype interference, was recovered from the Swinhoe pheasant and Chinese quail viruses. The Mongolian pheasant and Chukar viruses did not yield isolatable leukosis helper virus. Helper activity and spontaneously released endogenous virus were isolated from Chinese quail, Golden pheasants, and Ghighi pheasants, but not from the other species. Spontaneously released Chinese quail virus and the new RSV pseudotype from Chinese quail showed the same interference pattern. Plaques were produced by the pseudotypes from Chinese quail and Swinhoe pheasant cells, but not by any of the spontaneously produced viruses. Thus, the spontaneous viruses and their RSV pseudotypes are not genetically identical. (17 refs)

- 79-2144 Immunological Characterization of the RNA-dependent DNA Polymerase from Reticuloendothelial Virus.** (Eng) Moelling, K. (Max-Planck-Institut für Molekulare Genetik, D-1000 Berlin-Dahlem, W. Germany). *Med Microbiol Immunol (Berl)* 164(1/3): 115-118; 1977.

Immunological characterization of the RNA-dependent DNA polymerase (RDDP) from avian reticuloendotheliosis virus (REV) demonstrated that it was not related to the RDDP's from other known avian RNA tumor viruses. The structure, optimum ion requirements, and serology of the REV polymerase resembled those of the RDDP's from murine tumor viruses. However, much larger amounts of antiserum were required to inhibit the REV polymerase. Apparently, REV is not a genuine murine virus growing in avian cells; rather it seems to have undergone some process of adaptation to the new host. (6 refs)

- 79-2145 No Homology Detectable Between Marek's Disease Virus (MDV) DNA and Herpesvirus of the Turkey (HVT) DNA.** (Eng) Kaschka-Dierich, C. (Institut für klinische Virologie der Universität, Loschgestrasse 7, D-852 Erlangen, W. Germany); Bornkamm, G. W.; Thomssen, R. *Med Microbiol Immunol (Berl)* 165(4): 223-239; 1979.

The relatedness of four strains of Marek's disease virus (MDV) and two strains of herpesvirus of turkey (HVT) was analyzed by gel electrophoresis of viral DNA digested by site-specific endonucleases and by filter hybridization of viral DNA with complementary RNA (cRNA). The four MDV strains (1 pathogenic, 1 attenuated, and 1 apathogenic) showed fragment patterns completely different from those of the two HVT strains upon digestion of the viral DNA with *Bam*HI, *Eco*RI, *Hind*III, *Hpa*I, and *Xho* and separation of the fragments on agarose gels. Among the four MDV strains, the cleavage patterns showed great similarities as well as some slight differences. This was also true for the HVT strains. Filter hybridization of viral DNA with labeled cRNA prepared from MDV (strain GA) DNA or from HVT (strain PH-THV1) DNA HVT revealed no cross-hybridization between the MDV and HVT strains. It is estimated that the amount of homologous sequences in the MDV and HVT strains must be <3%-5% of the whole genome. This result was not expected, since both types of viruses are known to be antigenically related. (29 refs)

- 79-2146 Detection of Lucke Herpes Virus Antigens in Infected Frog Pronephric Cells.** (Eng) Tweedell, K. S. (Dept. Biology, Univ. Notre Dame, Notre Dame, IN, 46556); Mizell, M. *Arch Virol* 59(3): 239-249; 1979.

Antiserum to purified Lucke tumor herpes virus (LTHV) was used to detect Lucke herpes virus antigens in frog pronephric

(WMPA) cells infected with herpes virus derived from Lucke renal carcinomas of *Rana pipiens*. After application of LTHV antiserum, specific indirect immunofluorescence appeared in the cytoplasm, but not the nuclei, of virus-infected cells cultivated at 25 or 9 C; the former temperature was optimum for cell cultivation, whereas the latter was in the permissive range for virus induction. Normal WMPA cells treated with LTHV antiserum demonstrated neither cytoplasmic nor nuclear fluorescence at 25 or 9 C. Newly infected cells, in addition to showing cytopathic effects in tissue culture, produced either nuclear or cytoplasmic fluorescence, and virus activity was corroborated by electron microscopy (EM). Later cell passages produced only cytoplasmic fluorescence. In one infection, distinct and singular cytoplasmic fluorescence was correlated with scattered cytoplasmic herpes viruses and with groups of dense granular aggregates in the nuclei, as demonstrated by EM. The data suggest that after the initial isolations and early viral passages of LTHV in the pronephric cells, virus replication was either essentially arrested in most cells or it continued at a level insufficient to cause general cell lysis. (14 refs)

- 79-2147 Virus Precursor Shedding from Mammary Tumor Cells.** (Eng) McClelland, A. J. (Lab. Veterinary Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY). *Nature* 277(5691): 13; 1979.

The precursor molecule (pre-gp 70) of murine mammary tumor virus (MuMTV) glycoproteins is shed uncleaved from the surface membrane of tumor cells in which it is synthesized. However, labeling studies have shown that pre-gp70 is not present on the surface of MuMTV-producing cells. This indicates that two populations of pre-gp70 may exist: one destined to be cleaved and inserted into the membrane for virus assembly, and one that is shed without cleavage. This shedding may help MuMTV-producing cells escape host immune defenses. (no refs)

- 79-2148 Integration and Transcription of Mouse Mammary Tumor Virus DNA in Rat Hepatoma Cells.** (Eng) Ringold, G. M. (Dept. Pharmacology, Stanford Univ. Medical Sch., Stanford, CA, 94305); Shank, P. R.; Varmus, M. E.; Ring, J.; Yamamoto, K. R. *Proc Natl Acad Sci USA* 76(2): 665-669; 1979.

The observation that mouse mammary tumor virus (MMTV) gene expression is not simply a function of the dosage of viral DNA sequences in infected rat hepatoma cells (HTC) prompted an investigation of the structure and organization of the viral sequences that are integrated into the host genome. HTC 4.1 cells were infected with MMTV at multiplicities of infection ranging from approx 10^1 to 10^5 particles/cell. It is known that HTC cells infected with MMTV acquire viral DNA that becomes covalently linked to the cell DNA. Infected cell DNA's were cleaved with restriction en-

donucleases, the DNA fragments were separated electrophoretically, and fragments containing viral sequences were identified by molecular hybridization. The data presented demonstrate that there are many sites in cell DNA into which MMTV DNA integrates, that the junctions between viral and cellular DNA occur within a limited portion of the viral genome, that clones that contain MMTV DNA do not necessarily produce viral RNA, and that the extent of transcription and glucocorticoid responsiveness of MMTV proviruses may be dependent on the site(s) in cell DNA in which the viral DNA resides. Although there are many integration sites for MMTV DNA in HTC cell DNA, there appears to be a unique site on the viral genome that becomes linked to cellular DNA. (33 refs)

- 79-2149 Integration of the DNA of Mouse Mammary Tumor Virus in Virus-infected Normal and Neoplastic Tissue of the Mouse.** (Eng) Cohen, J. C. (Dept. Microbiology and Immunology, Tulane Univ., New Orleans, LA, 70112); Shank, P. R.; Morris, V. L.; Cardiff, R.; Varmus, H. E. *Cell* 16(2): 333-345; 1979.

Restriction endonucleases that cleave the DNA of mouse mammary tumor virus (MMTV) at one site (Eco RI) and at several sites (Pst I, Sac I, and Bam HI) were used to study infection and mammary tumorigenesis in mice. Proviruses (PV's) acquired during infection of BALB/c mice foster-nursed by virus-producing C3H females could be distinguished from the MMTV PV's endogenous to uninfected BALB/c mice by the fragments generated with Pst I and Bam HI. It was found that lactating mammary glands as well as mammary tumors from BALB/cfC3H mice acquired MMTV DNA and that a minimum of approx 10% of normal glandular cells were infected. The new PV's appeared to be linked to cellular DNA of mammary tumors and infected lactating mammary glands within a limited region (0.2×10^6 daltons) of the viral DNA. The location of this region, based upon mapping studies with unintegrated MMTV DNA, suggests that the orientation of these PV's is colinear with linear DNA synthesized in infected cells and thus approx colinear with viral RNA. A large number of sites in the cellular genome can accommodate a new PV; the acquired PV's are rarely, if ever, found in tandem with each other or with endogenous PV's. However, random integration and integration into a large number of preferred sites in the host genome cannot be distinguished. Since Eco RI and Bam HI cleavage of DNA from each mammary tumor generates a unique set of viral-specific fragments, it is proposed that the tumors are composed principally of cells derived from a subset of the many infected cells in a mammary gland. This proposal is supported by the finding that Eco RI digestion of DNA from several transplants of a primary tumor yields a pattern characteristic of the primary tumor. (26 refs)

- 79-2150 Murine Mammary Tumor Virus Expression During Mammary Tumorigenesis in BALB/c Mice.** (Eng) Pauley, R. J. (Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030); Medina, D.; Socher, S. H. *J Virol* 29(2): 483-493; 1979.

Hormone-induced BALB/c hyperplastic alveolar nodule (HAN) lines, which were established from primary HAN induced in BALB/c mice by hormonal stimulation alone or in combination with 7,12-dimethylbenz(a)anthracene (DMBA), and mammary tumors that arose in the HAN lines were examined for murine mammary tumor virus (MuMTV) expression. MuMTV expression was quantitated by molecular hybridization with a complementary DNA (cDNA) probe representative of the MuMTV genome. The D1 and D2 HAN lines, which originated in mice that had pituitary isografts alone (D2) or in combination with estradiol-17 β (D1), contained detectable amounts of hybridizable MuMTV sequences. MuMTV RNA sequences were also observed in 5/6 transplanted BALB/c mammary tumors examined. The D1 HAN line and the mammary tumors that arose from it contained approx 0.01% MuMTV-specific RNA sequences. The D2 HAN line and its mammary tumors contained appreciable amounts of MuMTV RNA, approx 0.13% of the total cellular RNA, a level that was similar to that in spontaneous mammary tumors from BALB/cfC3H mice. The D2 HAN line as well as the D2, C4 (hormone- + DMBA-induced), and CD8 (DMBA-induced) mammary tumors accumulated RNA that was apparently homologous to most of the MuMTV genome. Thermal denaturation of hybrids indicated extensive sequence homology between the MuMTV cDNA and hybridizable RNA in the BALB/c HAN lines and mammary tumors. A low level of C-Type viral RNA was observed in the BALB/c HAN lines and most mammary tumors by molecular hybridization with a cDNA to Moloney murine leukemia virus. These data demonstrate that MuMTV sequences are frequently expressed in hormone-induced BALB/c HAN lines and the mammary tumors derived from them and in the ductal hyperplasias induced in BALB/c mice by hormones and/or a chemical carcinogen. The transition from the preneoplastic to the neoplastic state in BALB/c mice does not appear to be due to a change in the steady-state levels of MuMTV RNA, since the hormone-induced HAN lines and mammary tumors had similar levels of hybridizable MuMTV RNA. (40 refs)

- 79-2151 Immunological Cross Reaction Between Sera from Patients with Breast Cancer and Mouse Mammary Tumor Virus.** (Eng) Imai, M. (Lab. Ultrastructure Res., Aichi Cancer Center Res. Inst., Kanokoden, Tashiro-cho, Nagoya 464, Japan); Yamada, C.; Saga, S.; Nagayoshi, S.; Hoshino, M. *Gann* 70(1): 63-74; 1979.

Sera from 89 Japanese breast cancer (BC) patients, 5 patients with benign mammary hyperplasia (BMH), 40 patients with neoplastic diseases other than breast cancer (NBC), and 68 healthy women (controls) were examined by immunofluores-

cence (IF) tests using cultured mouse mammary tumor tissue (MMT) producing mouse mammary tumor virus (MMTV). A positive reaction with MMT cells was obtained with 55.1% of the BC sera, 60% of the BMH sera, 30% of the NBC sera, and 26.5% of the control sera. Only the BC sera gave a significantly higher frequency of positive reactions than the control sera. Sera that were positive in the IF test with MMT cells did not react with MMTV-negative mouse cell lines. The distribution pattern of the specific fluorescence obtained with the positive sera was similar to that obtained with rabbit antiserum to A-type particles. The results of absorption studies and blocking tests also suggested that the reaction was due to antigenic components common to A- and B-type particles. The results of membrane IF tests suggested that some human sera also reacted with envelope antigen(s) of B particles. Antinuclear antibodies were found in 15.7% of the BC sera by IF; most of these sera did not contain antibodies that cross-reacted with MMTV. It is not known what role the antibodies to MMTV detected in human sera have in the development of BC. (31 refs)

- 79-2152 Structural Proteins of C-Type RNA Leukemia Viruses and Autoimmune Diseases of New Zealand Mice--Biochemical Analysis of MuLV Structural Proteins in the Serum and MuLV Cell-Surface Antigens Detectable by Endogenous Antibody.** (Jpn) Yoshiki, T. (Dept. Pathology, Sapporo City General Hosp., Sapporo, Japan); Hayasaki, T.; Itoh, T.; Shirai, T.; Ikeda, H.; Katagiri, M. *Virus* 28(2): 103-111; 1978.

The murine leukemia virus (MuLV) structural proteins in mouse serum were analyzed by affinity chromatography and sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and MuLV cell-surface antigens were characterized immunologically. Glycoprotein 70 (gp70)-related molecules in the serum of New Zealand mice occurred as an immune complex and consisted of three gp fragments with an approx mol wt of 53,000 (53K), 45K, and 32K, respectively. In contrast, gp70 isolated from the surface of infected cells was a single gp molecule with a wt of approx 70K. The mol wt of the major gp70 activity in serum fractionated by Sephadex gel filtration ranged from 120K to 140K. The minor gp70 activity was the same size as serum albumin. The results suggest that the three gp fragments of serum gp70 might have resulted from a specific transcriptional, translational, or post-translational process or from nonspecific proteolysis at susceptible sites. It is possible that a gp70-related molecule in the serum is a specific envelope-related gp that consists of three gp fragments with a mol wt 53K, 45K, and 32K, respectively, that serum gp70 is associated with host cellular components, or that it is present as a dimer. Pooled sera from 2- and 9-mo-old B/WF₁ mice were fractionated by Sephadex gel filtration. The major gp70 activity of 2-mo-old serum was found in fractions with a mol wt of 120-140K; that of 9-mo-old serum eluted mainly at the void volume. Most of the gp70-related molecules in the serum of the aged mice were probably present as immune complexes. In attempts to identi-

fy the molecule(s) bearing the antigenic determinants for endogenous antibody to MuLV or Gross-MuLV natural antibody (GNA), ¹²⁵I-labeled MuLV proteins were subjected to immunoprecipitation with GNA-positive mouse sera. SDS-PAGE of the resulting precipitates revealed that the major molecule bearing antigenic determinants for GNA was p(85), the precursor polypeptide of the MuLV core structural proteins p30, p15, and p10. (19 refs)

- 79-2153 Search for Type C Virus-Like Information in Normal, Benign and Malignant Human Prostatic Tissues.** (Eng) Kouttab, N. M. (Dept. Molecular Carcinogenesis and Virology, The Univ. Texas System Cancer Center, M.D. Anderson Hosp. Tumor Inst., Houston, TX, 77030); Bowen, J. M.; Dmochowski, L.; vonEschenbach, A.; Bracken, R. B.; Johnson, D. *Tex J Science* 30(5, Suppl): 139-148; 1978.

A competition radioimmunoassay (RIA) for C-type virus interspecies p30 antigen was used to determine whether murine leukemia virus (MuLV) p30-like antigens were present in normal, benign hyperplastic (BHP), or malignant (PCa) human prostate. Five of 17 BHP and 4/22 PCa tissue extracts were positive for the interspecies p30 antigen, but not for intraspecies p30 antigen. None of 10 normal tissue extracts was positive for either antigen. The positive results obtained with the BHP and PCa tissues were specific and apparently not due to enzymes such as proteases. Thus, it may be possible to separate RIA reactions that are specific for p30 interspecies antigen from reactions that may be due to protease activity. The data suggest that C type-like viral information may be present in human BHP and PCa tissues. (19 refs)

- 79-2154 Analysis of the Genomes of Leukemia Viruses of the AKR Mouse.** (Eng) Rommelaere, J. (Dept. Biology, Center Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139); Faller, D. V.; Hopkins, N. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 561-575; 1978.

The RNA genomes of the AKR mouse ecotropic N-tropic viruses Akv-1 and Akv-2, and four recombinant mink cell-focusing (MCF) viruses were studied by T1 RNA fingerprinting and oligonucleotide mapping. The MCF viruses were shown to share 75% of their large T1-resistant oligonucleotides with Akv-1 and -2 and to possess some large oligonucleotides not found in Akv viruses. Each MCF isolate differed in the number of large T1 oligonucleotides shared with Akv and in the number of MCF-specific oligonucleotides that it possessed. The Akv oligonucleotides missing in MCF fingerprints and MCF-specific oligonucleotides not found in Akv T1 fingerprints were clustered at corresponding regions of the Akv and MCF genomes in pooled data maps, as would be expected if MCF viruses arise by recombination involving an Akv virus. The biological properties of MCF

viruses indicated that they possess altered glycoprotein 70 (gp70) proteins relative to the Akv viruses. At least three, and possibly four, of the MCF isolates are missing Akv oligonucleotides starting at oligonucleotide map position 21. These observations suggest that the portions of the Akv and MCF genomes corresponding to map positions 21-27 contain sequences that code for gp70 and that are involved in determining the host range of the virus. It has been suggested that MCF's, rather than the ecotropic viruses, are the 'real' leukemogens in leukemia-susceptible mice and that the presence of a recombinant gp70 protein on the surface of lymphocytes may be the cause of their alteration to a transformed phenotype. (22 refs)

- 79-2155 AKR-MuLV-associated Cell Surface Antigens.** (Eng) Ihle, J. N. (Basic Res. Program, NCI Frederick Cancer Res. Center, Frederick, MD, 21501); Longstreth, J. D.; Pazmino, N. H.; McLellan, W. L.; Hanna, M. G. *Med Microbiol Immunol (Berl)* 164(1/3): 179-195; 1977.

The expression of AKR murine leukemia virus (MuLV)-associated cell-surface antigens was studied using antisera produced by immunization with either intact virus or virus-replicating cells. The type specificity of rabbit antisera to the purified viral antigens of AKR virus was indicated by reaction of each antiserum with its homologous protein and not with other virion components, by the inability of the antisera to neutralize Rauscher leukemia virus (RLV), and by the inability of the antisera to react significantly with the purified, iodinated RLV glycoprotein gp71. Titration data using purified AKR proteins indicated that they are excellent reagents for analyzing antigens recognizable by autogenous immune or monospecific hyperimmune sera. The specificity of the reactivities of the monospecific antisera to the individual AKR proteins was established by radioimmunoassay, and thus the distinctive reactivities could be used to characterize the expression of virus-associated antigens on the surface of virus-infected cells. The results using these specific reagents demonstrated that of the virion components examined, only gp71 and p12 were consistently expressed on the cell surface. The anti-AKR gp71 also labeled the virion sites on Gross leukemia virus-positive (G+) cells; the anti-AKR p12 labeled only the cell-surface sites of G+ cells. There are no data to explain why antibody to p12 recognizes the cell surface but not the virion. The results indicate that the expression of viral proteins gp71 and p12 on tumor cell surfaces may be a widespread phenomenon. (29 refs)

- 79-2156 Transfection by Exogenous and Endogenous Murine Retrovirus DNAs.** (Eng) Copeland, N. G. (Sidney Farber Cancer Inst., Boston, MA, 02115); Cooper, G. M. *Cell* 16(2): 347-356; 1979.

DNA transfection was used to study the endogenous re-

trovirus genomes inherited by uninfected mouse cells. Quantitative assays for infectious DNA's of ecotropic (ET) and xenotropic (XT) murine leukemia viruses (MuLV's) were developed using donor DNA's of cells that were exogenously infected with ET Moloney, AKR, or BALB MuLV's or with XT AKR, BALB, or NZB MuLV's. The DNA's of cells exogenously infected with ET MuLV's had specific infectivities of approx 0.5 infectious unit (IU)/ μ g DNA in transfection assays on NIH/3T3 cells. The DNA's of cells exogenously infected with XT MuLV's had specific infectivities of approx 0.2 IU/ μ g DNA in transfection assays on mink CCL64 cells. In contrast, the DNA's of uninfected NIH/3T3, BALB/3T3, and AKR-2B mouse cells were noninfectious when assayed for infectious endogenous ET MuLV DNA's (< 0.001 IU/ μ g DNA). Similarly, the infectivities of XT MuLV DNA's of uninfected NIH/3T3, BALB/3T3, AKR-2B, and NZB-Q mouse cells were > 100 -fold lower than the infectivities of DNA's of XT MuLV-infected cells. Furthermore, the DNA's of BALB/3T3 cells transformed by Kirsten murine sarcoma virus (MSV) or by simian virus 40 (SV40) were noninfectious for ET or XT MuLV, although these cells contained infectious transforming DNA's of MSV or SV40. The endogenous MuLV genomes of uninfected mouse cells thus appeared to differ from the MuLV proviruses of MuLV-infected cells. These results are consistent with the hypothesis that endogenous MuLV genomes are linked to cellular DNA sequences that result in both inefficient transcription of endogenous MuLV genomes and the reduced infectivity of endogenous MuLV DNA's in transfection assays. (56 refs)

- 79-2157 Quantitative Measurement of Intracellular RNA Genomes of Rauscher Murine Leukemia Virus by Competition Hybridization in DNA Excess.** (Eng) East, J. L. (Dept. Molecular Carcinogenesis, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Chan, J. C.; Bartlett, R. J.; Knesek, J. E. *J Virol* 29(2): 818-824; 1979.

The technique of competition hybridization in DNA excess was used to determine the intracellular distribution of RNA genomes of Rauscher murine leukemia virus and to determine the proportion of polyadenylated (poly A+) and non-polyadenylated (poly A-) viral RNA genomes that exist in total cellular RNA. The retrovirus-producing JLS/V5 cell line derived from BALB/c mouse spleen-thymus cells was used as the source for viral and intracellular RNA. An examination of subcellular RNA fractions revealed that 59% of intracellular viral RNA genomes were associated with the nuclear-enriched fraction, 41% with the cytoplasmic fraction, and 18% with the polysomal-enriched fraction. Also, an analysis of total cellular RNA disclosed that 20% of intracellular viral RNA genomes were poly A+ and 80% were poly A-. (29 refs)

- 79-2158 Regulation of Erythroid Differentiation: Characterization of Rauscher and Friend Virus-transformed Proerythroid Cells.** (Eng) Miao, R. M. (Life Sciences Div., SRI International, Menlo Park, CA, 94025); Fieldsteel, A. H. *Proc Soc Exp Biol Med* 160(1): 24-27; 1979.

The regulation of erythroid differentiation in proerythroid cell lines transformed by Friend virus (FV-BALB and FV-BDF₁) and Rauscher virus (RV-187 and RV-133) was studied. The benzidine assay for Hb was used to determine differentiation. RV-133 and RV-187 were induced to differentiate in the presence of eight known inducers: dimethyl sulfoxide, dimethylformamide, N-methylformamide, pyridine-N-oxide, butyric acid, hypoxanthine, acetamide, and N-methylpyrrolidone (NMP). The level of differentiation and the dose responses were different for the two cell lines and the various inducers. The FV-BALB line responded to only one of these inducers, NMP, even when the other inducers were added in cytotoxic concentrations. The second FV-transformed cell line, FV-BDF₁, did not respond to any of the inducers, even in cytotoxic concentrations. (27 refs)

- 79-2159 The Resistance of G Mouse Fibroblasts to Murine Leukemia Virus Infection.** (Eng) Kai, K. (Dept. Genetics, Inst. Medical Science, Univ. Tokyo, Shirokanedai, Minato-ku, Tokyo 108, Japan). *Jpn J Exp Med* 48(5): 459-462; 1978.

Mouse strain G cells, which are resistant to N- and NB-tropic Friend leukemic viruses (FLV's), FLV-susceptible DDD mouse cells, Fv-1 restricted BALB/c mouse cells, and non-permissive chick C/BE cells were examined for adsorption and penetration of ³²P-labeled N-tropic FLV. G mouse cells permitted viral adsorption and penetration as efficiently as the other mouse cells. The nonpermissive chick cells permitted adsorption as efficiently as mouse cells early after infection, but later the adsorption rate became slower. The chick cells also permitted penetration at a slower rate than mouse cells. Thus, the resistance of G mouse cells is not expressed in the adsorption or penetration steps. In the XC plaque assay, plaques in the G mouse fibroblasts were markedly smaller than those in other mouse fibroblasts, suggesting that there may be an inefficient propagation of the virus to surrounding cells. G, DDD, and BALB/c mouse embryo cells were infected with N-tropic FLV at a multiplicity of infection of 0.003, and the virus-producing cell population was estimated at intervals after infection. In G mouse cells, the increase in the virus-producing cells 6 days after infection was < 3 -fold, but in the DDD and BALB/c mouse cells the increase was 70-fold. These results suggest that the restriction of G mouse fibroblasts to MuLV is not in the first cycle of infection but in the propagation of the virus to the surrounding cells. (14 refs)

79-2160 Transformation of DBA/2 Mouse Fetal Liver Cells Infected In Vitro by the Anemic Strain of Friend Leukemia Virus. (Eng) Golde, D. W. (Div. Hematology and Oncology, Univ. California Sch. Medicine, Los Angeles, CA, 90024); Bersch, N.; Friend, C.; Tsuei, D.; Marovitz, W. *Proc Natl Acad Sci USA* 76(2): 962-966; 1979.

This study was designed to determine whether Friend leukemia virus (FLV) can transform hematopoietic cells in vitro and whether spleen focus-forming virus (SFFV) is essential for that event to occur. Fetal liver cells of DBA/2 mice were infected with the anemic strain of FLV (FLV-A), which has no SFFV activity. The infected cells were grown in medium with or without erythropoietin. Transformed lines were isolated only from the infected cultures that had been treated with erythropoietin at the time of their initiation. The properties of three permanent cell lines in serial passage for > 2 yr are described. Each has an aneuploid karyotype. Only the immature hematopoietic cells of the first line have metacentric chromosomes. They grow in suspension, as do the erythroleukemic lines derived from leukemic spleens of FLV-infected mice, and clone on agar. They produce tumors resembling reticulum cell sarcomas upon sc inoculation into syngeneic hosts. Stimulation of differentiation induced after treatment with dimethyl sulfoxide identifies the cells of the first line as being erythroid in origin. The two other lines are adherent and epithelioid in appearance. These lines may have originated from the nonhematopoietic cells present in fetal liver. No tumors were produced after the sc inoculation of 10⁶ cells. All three lines synthesize virus. The virus is attenuated for leukemogenicity and has no SFFV activity. The transforming event appears to be specific, because fetal liver cells from C57BL/6 mice, which are resistant to the induction of leukemia by FLV, were not affected by the virus. Malignant transformation of erythroid cells by FLV-A in vitro confirms the in vivo findings that SFFV may not be a necessary prerequisite for the induction of erythroleukemia in susceptible hosts. (27 refs)

79-2161 The State of the Globin Gene in Friend Erythroleukemia Cells. (Eng) Dube, S. K. (Sch. Medicine, Yale Univ., New Haven, CT, 06510); Wallace, R. B.; Bonner, J. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book A), 528 pp.; 311-317; 1978.

Friend-virus-infected cells susceptible to induction (line FSD 3) and resistant to induction (line F4+) were studied before and after induction by dimethyl sulfoxide (DMSO) to determine whether the globin gene is switched off during transformation and switched on by inducers. The DNA of the template-active fraction of induced and uninduced FSD3 cell chromatin was enriched seven-fold over whole-cell DNA for the globin gene sequence, the enrichment being essentially identical in the DNA of induced and uninduced cells. Template-active DNA from F4+ cells contained barely detectable levels of the globin gene sequence. Also, the F4+ cells did not suffer a deletion of the globin gene, as the tem-

plate-inactive DNA showed normal saturation hybridization with globin complementary DNA. The data indicate that the globin gene in Friend cells is in a transcriptionally active configuration in both induced and uninduced cells. (31 refs)

79-2162 Rosettes from Friend Leukemia Virus Envelope: Preparation and Physicochemical and Partial Biological Characterization. (Eng) Schneider, J. (Forschergruppe Tumorummunologie, Stefan-Meier-Strasse 8, D-7800 Freiburg im Breisgau, W. Germany); Schwarz, H.; Hunsmann, G. *J Virol* 29(2): 624-632; 1979.

Rosette-shaped particles containing mainly glycoprotein gp85 were isolated from the envelope of Friend leukemia virus and characterized. The isolation procedure comprised lysis of the virion by Triton X-100, affinity chromatography on concanavalin A-Sepharose, and velocity sedimentation. The rosettes displayed a mean sedimentation constant of 32S and a buoyant density of 1.21 g/ml. They contained 1% Triton X-100 and about 2% phospholipid. Gp85 was identified by polyacrylamide electrophoresis, staining with PAS reagent, and immunoprecipitation with antisera against Friend leukemia virus gp71 and p15(E). The rosettes completely blocked the cytotoxicity of the gp71 antiserum, and their ability to hemagglutinate was inhibited by antibodies to gp71. (32 refs)

79-2163 Sequential Gene Expression During Induced Differentiation of Cultured Friend Erythroleukemia Cells. (Eng) Obinata, M. (Lab. Viral Oncology, Cancer Inst., Tokyo 170, Japan); Kameji, R.; Uchiyama, Y.; Ikawa, Y. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book A), 528 pp.; 319-334; 1978.

Clonal cell lines derived from the T3-C1-2 Friend erythroleukemia (FE) line were used to study sequential gene expression during dimethyl sulfoxide (DMSO)-induced differentiation. Nucleic acid hybridization indicated that none of the variants of FE cells accumulated globin messenger RNA (mRNA) in the cytoplasm or nucleus in the uninduced condition and that with the addition of DMSO, globin mRNA accumulation in the cytoplasm and nucleus increased exponentially. Thus, posttranscriptional regulation was not involved in globin induction in these cells. Three frequency classes of mRNA were identified in uninduced FE cells: the first included approx 5 sequences, the second approx 400, and the last approx 9,680. Similar results were obtained in induced cells, these RNA sequences representing about 0.58% of the total unique sequences of the whole mouse genome. About 5,400-5,700 genes, representing approx 0.31%-0.34% of the mouse genome, were constitutively expressed throughout the course of differentiation; approx 3,000 genes were expressed and 4,400 were inactive during differentiation. Alteration of globin, inducible, suppressible, and common mRNA sequences was dependent on the induction of dif-

ferentiation. Only inducible messages of FE cells remained in the mouse reticulocytes; common messages disappeared during the maturation of erythroid cells. Reticulocyte non-globin messages were not expressed in FE cells. (38 refs)

- 79-2164 Genetic and Sialylation Sources of Heterogeneity of the Murine Leukemia Virus Membrane Envelope Glycoproteins gp69/71.** (Eng) Murray, M. J. (Dept. Biochemistry, Sch. Medicine, Univ. Oregon Health Sciences Center, Portland, OR, 97201); Kabat, D. J. *Biol Chem* 254(4): 1340-1348; 1979.

The heterogeneity of the membrane envelope glycoprotein of murine leukemia viruses (MuLV's) was investigated. When analyzed by polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate, this glycoprotein frequently separates into two components that have been termed gp69/71 because they migrate in the gels with an apparent mol wt of 69,000 and 71,000, respectively. Cloning experiments with MuLV produced by cultured Eveline cells (derived by infection of STU mouse cells with Friend MuLV) indicated that gp69 and gp71 are encoded by separate, closely related viral genomes that may frequently become incorporated into heterozygous virus particles. This and other evidence demonstrates that the size difference between gp69 and gp71 is caused by a difference in the amino acid sequences of their polypeptide chains. The gp69 and gp71 glycoproteins also have extensive isoelectric point microheterogeneity that can be reduced by removal of sialic acids with neuraminidase. Analyses of D-[³H]glucosamine-labeled glycopeptides by anion-exchange chromatography, gel filtration, and high-voltage paper electrophoresis indicated that the envelope glycoproteins are glycosylated at several sites. Apparently, the glycoproteins contain several complex oligosaccharides that are heterogeneously sialylated and at least two other relatively small neutral oligosaccharides. It is concluded that the heterogeneity of the envelope glycoprotein of MuLV's is due to at least two factors, a genetic heterogeneity caused by multiplicity of viral genomes and a variability in the numbers of sialic acid residues attached to oligosaccharides. (69 refs)

- 79-2165 Persistence and Pathogenicity of Defective Friend Spleen Focus-Forming Virus. Decreased Transplantability of Hemopoietic Cells as a Marker for Preleukemic Change.** (Eng) Eckner, R. J. (Dept. Microbiology, Boston Univ. Sch. Medicine, Boston, MA); Hettrick, K. L. *J Exp Med* 149(2): 340-357; 1979.

The oncogenic potential of purified defective Friend spleen focus-forming virus (SFFV) in mice was studied. A latent form of persistent infection was established in susceptible adults inoculated with SFFV purified free from standard leukemia-inducing helper virus (LLV-F). Initially, SFFV could be rescued directly to form splenic foci of malignant erythropoiesis in mice, but after approx 30 days, SFFV could

not be rescued after inoculation of LLV-F. This indicated that persistently infected (SFFV+) mice were either immune to exogenous helper virus or able to express SFFV-associated defective-interfering (DI) function(s). SFFV rescued by LLV-F from persistently infected normal and transformed hemopoietic cells was able to induce polycythemia in adult mice, and transplantable SFFV-induced erythroleukemic cells could be retrieved from persistently infected, histologically normal mice. The duration of SFFV persistence in normal spleen tissue suggests that the SFFV provirus resides in either a long-lived or pluripotent hemopoietic cell. Cell-surface alterations in persistently infected cells preceded the overt development of Friend leukemia and facilitated the definition of an SFFV preleukemic phase. Hemopoietic cells harboring a rescuable SFFV failed to proliferate when inoculated into lethally irradiated, syngeneic adult mice, whereas the transformed progeny of preleukemic cell populations and spleen cells transformed by the Friend virus complex (cells replicating both SFFV and LLV-F) were not rejected. Thus, histologically normal SFFV+ preleukemic cells apparently express an antigen recognition site that is not present on overtly transformed cells and that may be a pertinent surveillance target for host antileukemogenic reactions. (54 refs)

- 79-2166 The Effect of the Fv-2r Gene on Spleen Focus-forming Virus and on Embryonic Development.** (Eng) Steeves, R. A. (Dept. Genetics, Albert Einstein Coll. Medicine, Bronx, NY, 10461); Lilly, F.; Steinheid-er, G.; Blank, K. J. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 591-600; 1978.

The mechanism of the resistance to spleen focus-forming virus (SFFV) controlled by the Fv-2r gene was investigated in DBA/2 and partially congenic D2.Fv-2r and D2.Fv-1b mice. Following injection of Friend erythroleukemia virus (FV), D2.Fv-2r mice were only slightly more resistant to the expression of FV-infected cells than were D2.Fv-1b mice. This does not account for the complete resistance of D2.Fv-2r mice to spleen colony formation and is contrary to a preliminary hypothesis that the Fv-2r gene blocks malignant erythropoiesis. The possibility that the prime inhibitory effect of the Fv-2r gene could be mediated through an inhibition of SFFV replication was investigated. Spleen colony formation was shown to be an assay for infectious centers, dependent on the ability of virus released from inoculated cells to infect and replicate in adjacent cells. The principal inhibitory effect associated with the Fv-2r gene appears, therefore, to be directed against SFFV replication. Cell-mediated transfer of Fv-2r resistance was detected in two assay systems, one using a lethally irradiated host and the other Fv-1-restrictive, histocompatible F₁ hybrid recipients. In backcross experiments to produce a truly congenic strain, no Fv-2r/Fv-2r homozygotes were produced at any time during serial backcrossing to the DBA/2 strain. Thus, any gene(s) from the C57BL ancestor that might have been needed for survival of Fv-2r/Fv-2r homozygotes appeared to be lost. That such a protector gene exists and that its phenotypic expression is

dominant is demonstrated by the fact that homozygous Fv-2r/Fv-2r mice are produced normally when heterozygous DBA/2 backcross mice are mated to C57BL/6 mice. (19 refs)

- 79-2167 Immunoglobulin Synthesis by Lymphoid Cells Transformed In Vitro by Abelson Murine Leukemia Virus.** (Eng) Siden, E. J. (Dept. Biology, Center Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139); Baltimore, D.; Clark, D.; Rosenberg, N. E. *Cell* 16(2): 389-396; 1979.

A systematic study of immunoglobulin production by a large number of cell lines, each arising from a single focus of transformed bone marrow cells, was made. A sensitive radioimmunoprecipitation assay revealed that most cell lines derived by infection of murine bone marrow cells with Abelson murine leukemia virus (A-MuLV) synthesized a μ chain but no detectable light chain. Aside from this μ -only phenotype, lines that made only light chain, both chains, or no immunoglobulin-related polypeptides were also found. Two lines were studied in detail: one that made only μ chain and one that made only κ light chain. Synthesis of both polypeptides could be increased by modifying the culture conditions so as to decrease the growth rate of the cells. Although some κ chain secretion was observed, neither secreted nor surface μ was detected. It is suggested that the μ -only phenotype may be an early normal step in the pathway of B-lymphocyte maturation. (35 refs)

- 79-2168 Effects of Murine Leukemia Virus Infection on Differentiation of Hematopoietic Cells In Vitro.** (Eng) Teich, N. M. (Imperial Cancer Res. Fund Labs., Lincoln's Inn Fields, London WC2A 3PX, England); Dexter, T. M. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 657-670; 1978.

The interactions between murine leukemia virus (MuLV) variants and differentiating hematopoietic cells were studied in a culture system developed for long-term maintenance of murine bone marrow stem cells. Infection of marrow cultures from BDF₁ mice, which are genetically susceptible to viral erythroleukemia induction in vivo, by the Friend leukemia virus (FLV) complex changed the proliferation pattern and capabilities of the stem cells (CFU-S) and of the committed erythroid and granulocytic (CFU-C) precursor cells. Injection of syngeneic animals with infected cultured cells or with supernatants from these cultures induced erythroleukemia, showing that both the lymphatic leukemia virus (LLV) and the spleen focus-forming virus (SFFV) components of FLV replicated efficiently in the bone marrow cells. FLV-infected cultures derived from the genetically resistant C57BL mouse strain resembled uninfected control cultures. Tests of virus infectivity revealed that LLV replicated efficiently whereas SFFV did not. This suggests that the alterations in proliferative and differentiative capacity in the susceptible BDF₁ cul-

tures may be a function of SFFV expression and replication. In BDF₁ cultures infected with Moloney MuLV (MuLV-M), there was a rapid loss of CFU-S and CFU-C, suggesting that MuLV-M has a specific deleterious effect on early hematopoietic cells. Infection of BALB/c bone marrow cultures with Abelson MuLV resulted in the establishment of a transformed cell line that produced null-cell tumors in syngeneic or heterogeneic adult mice. (29 refs)

- 79-2169 Conformation of Moloney Murine Leukaemia Proviral Sequences in Chromatin from Leukaemic and Nonleukaemic Cells.** (Eng) Breindl, M. (Heinrich Pette-Institut für Experimentelle Virologie und Immunologie, Universität Hamburg, Martinistrasse 52, 2000 Hamburg 20, W. Germany); Jaenisch, R. *Nature* 277(5694): 320-322; 1979.

DNase I and micrococcal nuclease digestions were performed using chromatin from target (spleen) and nontarget (liver) cells from homozygous leukemic BALB/Mo mice. These mice carry the Moloney murine leukemia virus (M-MuLV) genome integrated into the DNA of all organs and develop a specific, thymus-derived leukemia in which expression of the M-MuLV genome is restricted to target tissues. M-MuLV-specific sequences were preferentially digested by DNase I in spleen cells but not in liver cells. However, in spleen cells in which amplification of the viral genome from one to three or four copies per haploid genome had taken place, only two of the copies were sensitive to DNase I. This suggests that the DNase I-sensitive sequences are transcriptionally active, whereas the resistant ones are inactive. Micrococcal nuclease did not preferentially digest viral sequences in target or nontarget tissues, indicating that the M-MuLV genomes in target and nontarget organs of BALB/Mo mice are organized in nucleosomal structures similar to those of the host cell DNA. Further, the data suggest that the multiple viral genome copies in tumor cells are integrated into the host cell genome and are not present as free proviral DNA. Unintegrated proviral DNA did not contribute to the DNase I-sensitive fraction of the M-MuLV-specific sequences. (17 refs)

- 79-2170 Structure of the Murine Leukemia Virus Envelope Glycoprotein Precursor.** (Eng) Witte, O. N. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139); Wirth, D. F. *J Virol* 29(2): 735-743; 1979.

The glycosylated *env* gene precursor (Pr80*env*) of Moloney murine leukemia virus was isolated by selective immunoprecipitation, and its structure was examined by treating infected NIH/3T3 cells for 3 hr with 10 or 100 μ g/ml tunicamycin. Use of the drug tunicamycin to inhibit nascent glycosylation or specific cleavage with endoglycosidase H (endo H) demonstrated that the precursor contained an apo-

protein with a mol wt of 60,000. The finished virion glycoprotein (gp70) was largely resistant to the action of endo H. Chromatography of the glycopeptides of Pr80env in conjunction with endo H digestion studies suggested that the precursor contained two distinct major glycosylation sites. Analysis of partial proteolytic cleavage fragments of Pr80env before and after endo H treatment placed the two glycosylation sites within a 30,000-dalton region of the apoprotein sequence. Kinetic experiments showed that carbohydrate processing as well as proteolytic cleavage are late steps in the maturation of Pr80env. (38 refs)

- 79-2171 Genes Controlling Receptors for Ecotropic and Xenotropic Type C Virus in *Mus cervicolor* and *Mus musculus*.** (Eng) Marshall, T. H. (Lab. Viral Carcinogenesis, NCI, Bethesda, MD, 20014); Rapp, U. R. *J Virol* 29(2): 501-506; 1979.

Gene loci controlling cell-surface receptors for murine leukemia virus (MuLV) were studied by infecting murine x Chinese hamster hybrid cells with three C-type viruses, two ecotropic (Moloney and M813 MuLV) and one xenotropic (Mol/8155). Hybrids that exclusively segregate murine chromosomes were made by fusing *Mus cervicolor* and *Mus musculus* lymphocytes to hamster fibroblasts. Sensitivity to Moloney MuLV infection and specific binding of the envelope glycoprotein of Rauscher MuLV (gp70) cosegregated, which implies that the gp70 binding site and Moloney receptor are genetically as well as physically linked and confirms that sensitivity to MuLV infection in the hybrids is controlled by surface receptors. Isozyme analysis revealed that the gene controlling gp70 binding and Moloney MuLV infection resides on chromosome 5 in both species. With the possible exception of one clone, no evidence was found for a proviral integration site independent of chromosome 5. Evidence is presented for additional unlinked ecotropic and xenotropic receptors independent of chromosome 5. (25 refs)

- 79-2172 A Receptor-mediated Model of Viral Leukemogenesis: Hypothesis and Experiments.** (Eng) McGrath, M. S. (Lab. Experimental Oncology, Dept. Pathology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305); Weissman, I. L. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 577-589; 1978.

A quantitative virus-binding assay was used to investigate the frequency and specificity of murine leukemia virus (MuLV)-binding thymocytes during spontaneous AKR lymphomagenesis, in radiation-induced thymic lymphomas, and in virus-induced thymic lymphomas, in order to test the hypothesis of receptor-mediated viral leukemogenesis. Rhodaminated and fluoresceinated MuLV binding to various lymphoid cell populations was analyzed by the fluorescence-activated cell sorter to measure the frequency of cells binding either or both labeled MuLV's. Within the normal

thymus, 0.5%-3.0% of cells bore receptors for MuLV's, the majority of which appeared to be large cells. Most cells from an AKR lymphoma bound the AKR recombinant (mink cell focusing) virus MCF-247 but did not bind the Moloney murine sarcoma virus/murine leukemia virus complex [MSV(MLV)], but most cells from a Moloney lymphoma bound Moloney virus but did not bind the AKR virus. This indicates that each virus-induced lymphoma possesses receptors that can discriminate between the two viruses. In contrast, the radiation-induced lymphoma L691 bound both MCF-247 and MSV(MLV) to equally high degrees. L691 cells could be infected with MSV(MLV) and MCF-247 viruses, establishing a correlation between virus binding and virus penetration and infection. In the preleukemic period, most thymocytes produced MuLV virion proteins and expressed them as antigens; only small numbers of cells expressed MuLV receptors. Upon injection in 1-mo-old AKR mice, virus antigen-positive receptor-negative cells were not tumorigenic, whereas virus antigen-positive, receptor-positive cells were. These results support the receptor-mediated model of leukemogenesis. (13 refs)

- 79-2173 Immuno-prophylaxis and -therapy of C-Type Oncorna Viral Diseases in Mice and Cats.** (Eng) Schafer, W. (Max-Planck-Institut für Virusforschung, D-7400 Tübingen, W. Germany); Bolognesi, D. P.; de Noronha, F.; Fischinger, P. J.; Hunsmann, G.; Ihle, J. N.; Moennig, V.; Schwarz, H.; Thiel, H. J. *Med Microbiol Immunol (Berl)* 164(1/3): 217-229; 1977.

Leukemias and solid tumors caused by vertically transmitted endogenous and/or horizontally transferred exogenous C-type oncornavirus (OV's) can be significantly influenced by antiviral antibodies (ab's), particularly those against gp71. Ab's against all antigenic determinants of this viral surface component are operative in passive immunization. Thus, OV-induced tumors can be treated with a single antiserum whose success is due to combined action of the passively administered ab and an active immune response by the host. Active immunization can be achieved by immunization with gp71, but this evokes primarily type-specific responses. Active immunization can also be achieved by infection with OV followed by ab treatment. (15 refs)

- 79-2174 Rescue and Transmission of a Replication-defective Variant of Moloney Murine Leukemia Virus.** (Eng) Rein, A. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20014); Benjers, B. M.; Gerwin, B. I.; Bassin, R. H.; Slocum, D. R. *J Virol* 29(2): 494-500; 1979.

The rescue and transmission of a replication-defective variant of Moloney murine leukemia virus (MuLV) from a clone of mouse cells (8A) are described. Clone 8A supernatants normally contain approx 10^2 focus-forming units/ml of murine sarcoma virus (MSV) and 10^2 complementation plaque-form-

ing units/ml of defective ecotropic MuLV; ie particles that give rise to XC plaques in assay cells simultaneously infected with XC-negative, nondefective amphotropic MuLV as well as the test virus. Superinfection of clone 8A cells with amphotropic MuLV resulted in a 500-fold increase in the titer of ecotropic MuLV particles detected in the complementation plaque assay. This increase was accompanied by a similar rise in the titer of MSV and by the production of a high level of nondefective MuLV. Rescue of defective MuLV and MSV from clone 8A showed similar kinetics, indicating that a single mechanism underlies these two phenomena. The defective MuLV rescued from clone 8A could be transmitted to a fresh clone of normal mouse cells. Amphotropic MuLV superinfection of NP-N cells, which contain a non-plaque-forming variant of N-tropic MuLV, also increased the titer of particles registering in the complementation plaque assay. Thus, NP-N cells also contain a rescuable defective variant of ecotropic MuLV. Although the assay and rescue techniques were developed through work with clone 8A, their successful application to NP-N cells indicates that they are of general utility for detecting and studying defective variants of ecotropic MuLV. (31 refs)

79-2175 The Origin, Physical Map, and Coding Properties of the Kirsten Murine Sarcoma Virus and the Friend Strain of Spleen Focus-forming Virus. (Eng) Scolnick, E. M. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20014); Shih, T. Y.; Troxler, D. H.; Howk, R. S.; Young, H. A. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 535-552; 1978.

Studies of the structure, coding properties, and malignant potential of Kirsten murine sarcoma virus (Ki-MuSV), a recombinant virus derived from the Kirsten strain of murine leukemia virus (Ki-MuLV) and a replication-defective rat virus, and the Friend strain of spleen focus-forming virus (SFFV) are reviewed. The results of molecular hybridization and oligonucleotide fingerprinting indicate that Ki-MuSV has 60 nucleotides of Ki-MuLV sequences at the 5' end joined to 7,000 nucleotides of rat sequences, which, in turn, are joined to 1,000 nucleotides of Ki-MuLV sequences at the 3' end of Ki-MuSV. Thus, > 85% of Ki-MuSV is composed of rat genetic information. The malignant potential of the virus could be coded for only by the rat sequences or some combination of the rat and mouse sequences at the 3' end of the virus. A 30S RNA subunit has been identified in mouse cells that has many of the properties of the replication-defective rat virus. In in vitro translation experiments, the main proteins synthesized by Moloney murine leukemia virus RNA and Ki-MuLV RNA were a p67, a p40, and a p25. The major product synthesized with Ki-MuSV RNA and the RNA of the defective rat virus and of the defective mouse virus was a p50. SFFV was found to be a recombinant between a portion of Friend murine leukemia virus at the 5' and 3' ends with sequences related to mouse xenotropic viruses between. The xenotropic viral sequences may be responsible for the rapid leukemogenicity of SFFV. If the xenotropic se-

quences of SFFV are the 'leuk' gene, then a region of the rat sequences in Ki-MuSV might be the 'src' gene of that virus. (22 refs)

79-2176 Restriction Endonuclease Cleavage of Linear and Closed Circular Murine Leukemia Viral DNAs: Discovery of a Smaller Circular Form. (Eng) Yoshimura, F. K. (Center Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139); Weinberg, R. A. *Cell* 16(2): 323-332; 1979.

Both the unintegrated linear (form III) and closed circular (form I) viral DNA's obtained from JLS-V9 mouse cells infected with Moloney murine leukemia virus were cleaved by Sal I, Sma I, Bam HI, and Pst I restriction endonucleases. The resulting DNA fragments were ordered with respect to the 5' and 3' ends of the RNA genome by several techniques, including comparisons of the DNA fragments from cleavages of the linear and closed circular forms, double digestions using different combinations of enzymes, and the use of an RNA probe specific for the 3' end. DNA from Hirt extractions of infected cells yielded a discrete species of linear viral DNA whose size was determined by agarose gel electrophoresis to be 5.7×10^6 daltons. During characterization of the closed circular DNA, two form I DNA molecules were observed. The larger molecule was the same size as the linear DNA. The second molecule migrated faster on agarose gels and was the predominant species of the two closed circular DNA's. Restriction endonuclease maps show that this novel form I DNA is a smaller homogeneous species of viral DNA, missing about 600 nucleotides found in the linear and larger closed circular DNA molecules. The site of this missing DNA piece was determined to be at either one or both ends of the linear viral DNA. (35 refs)

79-2177 Oncogenic and Immunogenic Potential of Cloned HIX Virus in Mice and Cats. (Eng) Fischinger, P. J. (NCI, NIH, Building 41, Suite 400, Bethesda, MD, 20014); Ihle, J. N.; de Noronha, F.; Bolognesi, D. P. *Med Microbiol Immunol (Berl)* 164(1/3): 119-129; 1977.

HIX virus, a hybrid of the IC strain of Moloney murine leukemia virus and murine xenotropic virus (MuX), was tested for oncogenicity in newborn BALB/c and NIH Swiss mice and newborn kittens. Purified HIX virus, which had been grown in diploid cat embryo cells for three passages, induced lymphomas in both mouse strains. Only animals that had a histopathologic diagnosis of lymphoma were scored as positive. The actual incidence was probably > 50%. The same virus did not produce tumors in cats after up to 21 mo of observation. The mouse tumors were caused by HIX virus alone, because pure HIX virus was isolated from tumors without detectable eco- or xenotropic viruses. Terminal foci isolated from HIX-induced tumors in tissue culture behaved exactly as parental input virus in focus morphology,

group-specific antigens, serum factor susceptibility, and neutralization profiles. HIX may exist in BALB/c mice as an easily detectable high-titer virus, because MuX- or HIX-inactivating normal serum factor activity was reduced in tumor-bearing BALB/c mice. (19 refs)

- 79-2178 Biosynthesis of Rauscher Leukemia Virus Reverse Transcriptase and Structural Proteins: Evidence for Translational Control.** (Eng) Arlinghaus, R. B. (Dept. Biology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. & Tumor Inst., Houston, TX, 77030); Jamjoom, G. A.; Kopchick, J.; Naso, R. B. *30th Ann Symp Cancer Res* 271-295; 1978.

The possible existence of translational control over the expression of the Rauscher leukemia virus (RLV) genome was studied. Pulse-chase experiments indicated that viral precursor polypeptides are built up and processed at different rates. The chloromethyl ketone derivatives tolylsulfonyl-phenylalanyl chloromethyl ketone and carbobenzyloxyl-phenylalanyl chloromethyl ketone caused a relative enrichment of the 200,000-dalton virus-specific polypeptides (designated Pr1a+b) and a reversal of the ratio of the 80,000-dalton to the 70,000-dalton polypeptides. Pr1a+b contained determinants of both the group-specific antigens and reverse transcriptase (RT). This indicates that in RLV, the *gag* and *pol* genes are adjacent and can be translated as one polypeptide. Following pulse labeling of virus-infected cells, approx one-fifteenth as many RT sequences were made in the cell as p30 sequences, making it unlikely that the sole pathway of formation of both *gag* and *pol* gene products is by cleavage of the common precursors Pr1a+b. The formation of RT precursors appears to occur by cleavage of pre-formed Pr1a+b, whereas the formation of p30 precursors appears to follow different kinetics. With regard to the latter, an extremely fast cleavage or a nascent chain cleavage must be hypothesized. (55 refs)

- 79-2179 Influence of the Mouse Hepatitis Virus (MHV) Infection on the Growth of Human Tumors in the Athymic Mouse.** (Eng) Kyriazis, A. P. (Dept. Pathology, Univ. Cincinnati Coll. Medicine, 231 Bethesda Ave., Cincinnati, OH, 45267); DiPersio, L.; Michael, J. G.; Pesce, A. J. *Int J Cancer* 23(3): 402-409; 1979.

The growth characteristics and histologic appearance of tumors resulting from the transplantation of human tumor lines HEP-2 (laryngeal carcinoma) and SW480 (colon carcinoma) into pathogen-free and mouse hepatitis virus-infected athymic mice were studied. Sc or ip implantation of 1×10^6 neoplastic cells into pathogen-free animals resulted in tumor growth. Sc tumor transplants grew at the injection site, and they were surrounded by a capsule of connective tissue. The fibrovascular stroma supporting the neoplastic tissue was minimal, and infiltration of the tumor capsule was observed. Ip tumors

grew in a multifocal pattern, were not encapsulated, showed marked invasiveness, and metastasized. Sc tumors failed to grow in most hepatitis-infected animals that developed signs of hepatitis during the posttransplantation period, and the ip tumors did not grow at all. When larger numbers of HEP-2 tumor cells were inoculated ip, a few animals developed small, strictly localized tumor nodules with no local invasion or metastases. SW480 cells produced no tumors. No evidence supporting T-cell-mediated tumor rejection was obtained. It is concluded that the state of health of athymic mice is critical for the growth of human tumors and that it may account for the varied success in transplanting these tumors in nude mice. (21 refs)

- 79-2180 Tumor Angiogenesis Activity in Clonal Cells Transformed by Bovine Adenovirus Type 3.** (Eng) Tsukamoto, K. (Biological Res. Labs., Central Res. Div., Takeda Chemical Industries, Ltd., Osaka 532, Japan); Sugino, Y. *Cancer Res* 39(4): 1305-1309; 1979.

Four different lines of clonal cells transformed by bovine adenovirus type 3 (BAV3) and its oncogenic DNA fragments and the clonal normal counterparts of these lines were tested for tumor angiogenesis (TA) activity. TA activity was assayed by measuring the host-mediated vascular response of a chick embryo chorioallantoic membrane (CAM) to a cell suspension separated from the vascular bed by a Millipore filter. Angiogenesis activity due to an inflammation reaction of the CAM was prevented by corticosteroids. The four clonal transformed cell lines tested were TrD-5 and TrJE-6 (clonal lines of BALB 3T3 clone A31 cells transformed by the D and JE fragments of BAV3 DNA), NC1-TIC (derived from the NC1 clonal line of NIH Swiss 3T3 and transformed by BAV3), and BHK-T73 (clonal line of baby hamster kidney cells transformed by BAV3). All of the transformed cells had stronger TA activities than their clonal normal counterparts. Hepatoma B16 (solid form) sarcoma 180 (ascites and solid form), and Lewis lung tumor (solid form) also gave strong vascular responses in the TA assay. Studies with TrD-5 and A31 cells indicated that the expression of TA activity was dependent on cell dose and time. TA activity was destroyed by heating the cells. The finding of strong TA activities in TrD-5 and TrJE-6 cells, which were infected with DNA fragments that are only 16.1% and 11.9% respectively, of the BAV3 DNA, indicates that the increase in TA activity is controlled by the transforming gene of the virus. (15 refs)

- 79-2181 Humoral Antibody Response to Bovine Leukemia Virus Infection in Cattle and Sheep.** (Eng) Bex, F. (Dept. Molecular Biology, Universite Libre de Bruxelles, 67 rue des Chevaux, 1640 Rhode-St.-Genese, Belgium); Bruck, C.; Mammerickx, M.; Portetelle, D.; Ghysdael, J.; Cleuter, Y.; Leclercq, M.; Dekegel, D.; Burny, A. *Cancer Res* 39(3): 1118-1123; 1979.

Three serological methods were used to test 345 cattle from 7 herds with a history of lymphosarcoma for antibody to bovine leukemia virus (BLV) antigens. These three methods were immunodiffusion using a BLV glycoprotein with a mol wt of 60,000 (gp60) as antigen, and radioimmunoassay using a BLV gp60 and a BLV protein with a mol wt of 24,000 (p24) as antigen. The three tests gave the same results for 325 animals, with 240 being negative and 85 being positive. The results were variable in 10 cases. The gp60 antibody titers were systematically higher than the p24 antibody titers in bovine sera and milk as well as in the sera of experimentally infected sheep. In the latter case, antibodies to BLV antigens reached max values at the death of the animal in the tumor phase of the disease. Ratios of serum antiglycoprotein titer to milk titer varied between 4 and 117, showing that, if milk pools are to be used in surveys of BLV infection, use of very sensitive techniques of detection is mandatory. (39 refs)

79-2182 The Bovine Leukosis Virus. (Eng) Mussgay, M. (Federal Res. Inst. Animal Virus Diseases, Paul-Ehrlich-Strasse 28, D-7400 Tübingen, W. Germany); Dietzschold, B.; Frenzel, B.; Kaaden, O. R.; Straub, O. C.; Weiland, F. *Med Microbiol Immunol (Berl)* 164(1/3): 131-138; 1977.

The usefulness of some of the properties of bovine leukosis virus (BLV) in the serological diagnosis of enzootic bovine leukosis was determined. The properties investigated included the morphology, reverse transcriptase activity, and polypeptide pattern of BLV. The serological diagnosis of bovine enzootic leukosis may replace hematological examinations in the near future. (13 refs)

79-2183 Studies on the Polypeptides of Poxvirus. II. Comparison of Virus-induced Polypeptides in Cells Infected with Vaccinia, Cowpox and Shope Fibroma Viruses. (Eng) Ikuta, K. (Dept. Pathology, Res. Inst. Microbial Diseases, Osaka Univ., Yamada-kami, Suita, Osaka 565, Japan); Miyamoto, H.; Kato, S. *Biken J* 21(3): 77-94; 1978.

Virus-induced polypeptides (pp) in RK₁₁ cells infected with vaccinia, cowpox, and Shope fibroma viruses were examined by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis followed by autoradiography. At least 42 vaccinia virus-induced pp were identified among the pp of cells pulse-labeled with [³⁵S]-methionine and/or the pp of fractionated cells labeled with [¹⁴C]-leucine for 24 hr. They consisted of 15 pp (early pp) that were able to be synthesized in the presence of cytosine-1-β-D-arabinofuranosyl HCl and 27 pp (late pp) that were synthesized only in the absence of cytosine-1-β-D-arabinofuranosyl HCl. By the same procedure, at least 40 cowpox virus-induced pp (14 early pp and 26 late pp) and at least 31 Shope fibroma virus-induced pp (13 early pp and 18 late pp) were identified. Comparative

studies of virus-induced pp on the basis of migration during SDS-polyacrylamide gel electrophoresis revealed that 11 pp were early pp common to both vaccinia and cowpox viruses; 21 were late pp common to both vaccinia and cowpox viruses; 4 were early pp common to both vaccinia and Shope fibroma viruses; 7 were late pp common to both vaccinia and Shope fibroma viruses; 5 were early pp common to both cowpox and Shope fibroma viruses; 9 were late pp common to both cowpox and Shope fibroma viruses; 4 were early pp common to all three viruses; and 7 were late pp common to all three viruses. (17 refs)

79-2184 Vaccinia Virus Replication. I. Requirement for the Host-Cell Nucleus. (Eng) Hruby, D. E. (Dept. Microbiology, Health Sciences Center, State Univ. New York, Stony Brook, NY, 11594); Guarino, L. A.; Kates, J. R. *J Virol* 29(2): 705-715; 1979.

The ability of vaccinia virus (VV) to replicate in the absence of the host-cell nucleus was examined in several mammalian cell lines by cytochalasin B-induced enucleation techniques. Virus-infected enucleated cells (cytoplasts) prepared from BSC-40, CVC, and L cells were incapable of producing infectious progeny virus. The nature of this apparent nuclear involvement was studied in detail in BSC-40 cells. Modulations designed to maximize cytoplasmic integrity and longevity, such as reduction of the growth temperature and initial multiplicity of infection, did not improve virus growth in cytoplasts. Sodium dodecyl sulfate-polyacrylamide gel analysis of the [³⁵S]methionine pulse-labeled proteins synthesized in VV-infected cytoplasts demonstrated that both early and late viral gene products were being expressed at high levels and with the proper temporal sequence. VV cytoplasmic DNA synthesis, as measured by [³H]thymidine incorporation, peaked at 3 hr postinfection and was 70%-90% of control levels in cytoplasts. However, in the cytoplasts this DNA was not converted to a DNase-resistant form late in infection, which was consistent with the failure to isolate physical particles from infected cytoplasts. Treatment of VV-infected cells with 100 μg of rifampin/ml from 0 to 8 hr postinfection to increase the pools of viral precursors, followed by subsequent removal of the drug, resulted in a threefold increase in virus yield. This treatment had no effect on virus-infected cytoplasts. Finally, VV morphogenesis was studied under an electron microscope in thin sections of virus-infected cells and cytoplasts that had been prepared at various times during a single-step growth cycle. It was apparent that, although early virus morphogenetic forms appeared, there was no subsequent DNA condensation or particle maturation in the cytoplasts. These results suggest that VV requires some factor or function from the host-cell nucleus in order to mature properly and produce infectious progeny virus. (29 refs)

79-2185 Feline Sarcoma Virus-coded Polypeptide: Enzymatic Cleavage by a Type C Virus-coded

Structural Protein. (Eng) Khan, A. S. (Viral Oncology Program, Frederick Cancer Res. Center, Frederick, MD, 21501); Stephenson, J. R. *J Virol* 29(2): 649-656; 1979.

A purified 15,000-dalton (15K) Prague strain Rous sarcoma virus *gag* gene-coded structural protein, p15, was shown to enzymatically cleave the previously described 130K feline sarcoma virus (FeSV)-coded precursor polyprotein Pr130. Cleavage products included proteins ranging in mol wt from 12K to 110K. The specificity of this cleavage reactivity was indicated by the fact that, under similar conditions, neither purified C-type viral structural proteins nor nonviral proteins such as bovine serum albumin were cleaved to significant extents. Moreover, the feline leukemia virus *gag* gene-coded precursor polyprotein Pr65*gag* was efficiently cleaved, resulting in the generation of proteins of 30K (p30), 15K (p15), 12K (p12), and 10K (p10). Using enzymatically (p15) treated FeSV Pr130 as starting material, a major 72K cleavage product was purified and shown to contain the nonstructural component of FeSV Pr130. (22 refs)

79-2186 Immunosuppressive Properties of a Virion Polypeptide, a 15,000-Dalton Protein, from Feline Leukemia Virus. (Eng) Mathes, L. E. (Dept. Veterinary Pathobiology, Coll. Veterinary Medicine, Ohio State Univ., Columbus, OH, 43210); Olsen, R. G.; Hebebrand, L. C.; Hoover, E. A.; Schaller, J. P.; Adams, P. W.; Nichols, W. S. *Cancer Res* 39(3): 950-955; 1979.

Inactivated whole feline leukemia virus (FeLV) and subviral components of FeLV were analyzed for their inhibitory effect on concanavalin A (ConA)-stimulated lymphocyte blast transformation (LBT) using lymphocytes from specific pathogen-free cats. Inactivated FeLV inhibited LBT by 43% and a subfraction containing a 15,000-mol-wt peptide (p15) as its major component inhibited it by 41%; three other protein subfractions had no significant effects. Purified p15 inhibited LBT by 68%, but purified p27 inhibited it by only 18%. The inhibition was apparently not due to p15 cytotoxicity or to competition for Con A-binding sites. FeLV and FeLV p15 caused alterations in cell membrane function, as indicated by an up to 83% inhibition of the normal capping process. Cats inoculated with heat-killed FL-74 cells were protected from feline sarcoma virus (FeSV) challenge, but when p15 was added to the FL-74 cell vaccine, the incidence of progressive fibrosarcoma was significantly increased after FeSV challenge. The data support the hypothesis that the immunosuppression observed in cats infected with FeLV is mediated by FeLV p15. (25 refs)

79-2187 Feline Oncornavirus-associated Cell-Membrane Antigen: An FeLV- and FeSV-induced Tumor-specific Antigen. (Eng) Hardy, W. D. (Lab. Veterinary Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Zuckerman, E. E.; Essex, M.; MacEwen,

E. G.; Hayes, A. A. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 601-623; 1978.

The cell membranes of naturally occurring pet cat tumors and normal cat cells were tested for feline oncornavirus-associated cell-membrane antigen (FOCMA) to determine if it is unique to feline leukemia virus (FeLV)- and feline sarcoma virus (FeSV)-induced cat tumors. Of the 44 cats studied, 31 were infected with FeLV, whereas 13 were nonproducers. Twenty-seven cats had T-cell lymphosarcomas (LSA's), 6 B-cell LSA's, 10 mixed-cell LSA's, and 1 a null-cell LSA. Every LSA cell preparation tested had FOCMA in the cell membrane whether or not the LSA cells were replicating FeLV or were nonproducers. FOCMA was absent from the cell membranes of morphologically normal peripheral blood lymphocytes obtained from four of the FeLV-infected cats with LSA's and from five of the nonproducer cats with LSA's. Eight nonlymphoid cat tumors tested for FOCMA were negative, but granulocytic tumor cells from an FeLV-infected cat with myelogenous leukemia, tumor cells from an FeLV-infected cat with megakaryocytic leukemia, two fibrosarcoma cultures derived from cats with naturally occurring FeSV-induced fibrosarcomas, and a canine nonproducer sarcoma cell culture derived from a puppy with FeSV-induced sarcoma were all FOCMA-positive. FOCMA was not detected on any normal cells, even if they were actively producing FeLV. These studies have directly established that FOCMA is expressed only on cat cells transformed by FeLV or FeSV. The finding that FOCMA is expressed on granulocytic and megakaryocytic leukemic feline cells suggests that FeLV can transform cells other than lymphoid cells. (72 refs)

79-2188 Mobility of Lymphocyte Surface Membrane Concanavalin A Receptors of Normal and Feline Leukemia Virus-infected Viremic Felines. (Eng) Dunlap, J. E. (Dept. Pathology, Ohio State Univ., Columbus, OH, 43210); Nichols, W. S.; Hebebrand, L. C.; Mathes, L. E.; Olsen, R. G. *Cancer Res* 39(2): 956-958; 1979.

The virus-associated depression of concanavalin A (Con A) mitogenesis that accompanies feline leukemia virus (FeLV)-induced cat lymphoma was investigated by comparing the lymphocyte surface receptor mobility of normal cats to that of viremic diseased animals. The mechanics of feline lymphocyte receptor mobility were studied using fluorescein-conjugated Con A to quantitate lymphocyte capping. The results of a study of 21 disease-free animals showed that cat lymphocytes undergo appreciable Con A capping, with a mean capping rate of 17% under conditions developed in this study. In contrast, morphologically normal peripheral blood lymphocytes of six FeLV-infected viremic cats, with or without lymphoma, exhibited a mean capping rate of only 7%, significantly less than that of the control animals ($p < 0.005$). These findings suggest that a membrane-related lymphocyte deficiency accompanies the development of virus-induced lymphoma in the cat. (35 refs)

79-2189 Infection and Immunization of Cats with the Kawakami-Theilen Strain of Feline Leukemia Virus. (Eng) Salerno, R. A. (Div. Virus and Cell Biology Res., Merck Inst. Therapeutic Res., West Point, PA, 19486); Larson, V. M.; Phelps, A. H.; Hilleman, M. R. *Proc Soc Exp Biol Med* 160(1): 18-23; 1979.

The effects of viral dose, mode of transmission, and host age on the responses of specific-pathogen-free cats to the Kawakami-Theilen strain of feline leukemia virus (KT-FeLV) were studied. Injections of high doses of KT-FeLV (10^9 - 10^{12} virions) into 29 1- to 2-day-old kittens resulted in illness in 13. The sick kittens became moribund and showed other evidence of disease; FeLV was isolated from the peripheral blood lymphocytes of these, but not the healthy, kittens. Cytotoxic antibody against FeLV-infected FL74 feline lymphoid tumor cells developed in 10/16 non-viremic inoculated kittens, 6/15 nonviremic cats in contact with viremic kittens, and 0/13 viremic kittens. None of a group of 17- to 24-wk old cats became ill or developed viremia when inoculated with high doses of KT-FeLV, but nearly all developed cytotoxic antibody. In neither experiment did animals in contact with the inoculated cats become ill or develop viremia. Two cats were given six doses of formalinized FeLV vaccine im. One developed both neutralizing and cytotoxic antibody titers, and the other developed a cytotoxic antibody titer. The incidence of leukemia was 20% among the five offspring of these cats following challenge with KT-FeLV; the incidence of leukemia among eight kittens from unvaccinated queens was 88% following challenge. (25 refs)

79-2190 Human Humoral Antibodies Specific for Primate C-Type Viral Antigens. (Eng) Kurth, R. (Friedrich Miescher-Laboratorium der Max Planck-Gesellschaft, Spemannstrasse 37-39, D-7400 Tübingen, W. Germany); Schmitt, C. *Med Microbiol Immunol (Berl)* 164(1/3): 167-177; 1977.

Human sera were examined for the presence of natural antibodies directed against antigenic determinants of C-type virus structural proteins. Iodinated proteins from detergent-disrupted baboon endogenous virus (BEV) and replication-defective simian sarcoma virus (simian sarcoma-associated helper virus) [SSV(SSAV)] were used as antigens. The immune reactions appeared to be specific for virus antigens. Approx 50% of >100 normal sera tested recognized SSV(SSAV) antigens, and about 80% of the sera recognized BEV antigens. Individual sera precipitated one, two, or all three of the virus structural proteins p28, gp70, or p15. The immune reaction was mediated by human IgG, and preliminary experiments showed that IgM might also be involved. There was no immunological evidence that vertical virus transmission or active vertical antiviral immunization occurred. However, antiviral maternal IgG was transmitted into cord blood. (33 refs)

79-2191 A New Virion Precipitation Test for Oncovirus Envelope Antigens Which Detects Common Antigenic Determinants in Mammalian Type-C Viruses and Mason-Pfizer Monkey Virus. (Eng) Altstein, A. D. (D. I. Ivanovsky Inst. Virology, USSR Acad. Medical Sciences, Moscow, USSR); Zakharova, L. G.; Zhdanov, V. M. *Int J Cancer* 23(3): 424-433; 1979.

The virion precipitation test (VPT) was developed for the study of oncovirus (OV) envelope antigens based on the precipitation of intact virions by a double-antibody technique. The amount of precipitated virus was then determined by measuring its reverse transcriptase activity. Internal antigens of the virions were not precipitated. The method was used to study the relationship between the envelope antigens of 11 different OV's. Four groups of OV's having no cross-relationships in their envelope antigens were distinguished: mammalian C-type viruses and Mason-Pfizer monkey virus (M-PMV); murine B-type virus (mouse mammary tumor virus); bovine leukemia virus; and avian C-type viruses (Prague strain of Rous sarcoma virus). Within the first group, VPT demonstrated a broad cross-relationship. The following subgroups were distinguished within the group of mammalian C- and D-type viruses: murine C-type viruses, feline leukemia virus; endogenous feline C-type virus RD-114 and endogenous baboon C-type virus BK-CT, simian sarcoma virus, and M-PMV. Antibodies that reacted with the common determinants could not be removed by absorption with human cells and normal calf serum. This cross-reactivity could be selectively removed by absorption of the sera with the viruses. The common antigenic determinants may provide significant information concerning OV evolution. (22 refs)

79-2192 Mason-Pfizer Like Virus in Kidney Grafted Patients. (Eng) Thiry, L. (Institut Pasteur du Brabant, 1040 Brussels, Belgium); Sprecher-Goldberger, S.; Vandebussche, P.; Bossens, M.; Vereerstraten, P.; Hestermans-Medard, O. *Med Microbiol Immunol (Berl)* 165(4): 255-269; 1979.

Lymphocytes from kidney-graft patient were specifically stimulated to incorporate thymidine in vitro by mitomycin C-treated HeLa cells infected with a Mason-Pfizer-like virus (MPV). The thermolabile mutant of vesicular stomatitis virus (VSV tl) grown in the WBC of this patient produced pseudotypes that were neutralized by the patient's sera and by rabbit anti-MPV sera. Coculture of the patient's WBC with rabbit cornea cells (SIRC) yielded virus populations with dual properties: those of MPV plus those of another virus that was not typed serologically but possessed the biological properties of typical C particles. These virus populations were characterized by reverse transcriptase activity in the presence of Mn^{2+} and Mg^{2+} as well as by syncytium formation on both XC cells (rat cells with Rous genes) and KC cells (human cells carrying the Rous genome). The patient also had neutralizing antibodies to MPV, which were detected by inhibition of syncytium formation on KC cells and by neutraliza-

tion of the VSV tl (MPV) pseudotypes. These pseudotypes, which were obtained from two WBC cultures of the same patient, were not obtained with 18 other graft patients or with 13 healthy adults. MPV-like viruses could be latent in graft patients and activated by immunosuppressive drugs, or they may be introduced in the patients by the kidney graft or by the repeated blood transfusions. (38 refs)

- 79-2193 Transformation of Hamster Kidney Cells by Simian Papovavirus SA12.** (Eng) Valis, J. D. (Dept. Pathobiology, Johns Hopkins Univ. Sch. Hygiene and Public Health, Baltimore, MD, 21205); Strandberg, J. D.; Shah, K. V. *Proc Soc Exp Biol Med* 160(2): 208-212; 1979.

The transformation of hamster kidney (HK) cells by simian agent 12 (SA12 virus) was studied, as was the ability of transformed cells to produce tumors in syngeneic hosts. HK cells inoculated with SA12 showed transformation characterized by increased saturation density, altered morphology, loss of contact inhibition, increased growth rate, an indefinite life-span, reduced serum requirements for growth, an ability to grow in soft agar, and the presence of SA12-specific tumor (T) antigen. Neither infectious virus nor viral structural antigen was demonstrated by Sendai virus-induced fusion of transformed HK (SAHK-1) cells with permissive cells. SAHK-1 cells inoculated into weanling hamsters consistently produced tumors that were readily maintained by passage in hamsters. The cells appeared to become more tumorigenic after successive passage in hamsters. Pure adenocarcinomas, undifferentiated sarcomas, and mixed tumors containing both carcinomatous and sarcomatous elements were seen. SA12 T antibodies were detected in each of 16 sera from individual tumor-bearing hamsters. (9 refs)

- 79-2194 Detection of Herpes Simplex Virus Tumor-associated Antigen in Uterine Cervical Cancer Tissue. Five Case Studies.** (Eng) Notter, M. F. (Dept. Microbiology and Cell Biology, Pennsylvania State Univ., 101 S. Frear Bldg., University Park, PA, 16802); Docherty, J. J.; Mortel, R.; Hollinshead, A. C. *Gynecol Oncol* 6(6): 574-581; 1978.

Biopsy specimens from five patients with gynecologic cancers were examined for the presence of herpes simplex virus tumor-associated antigen (HSV-TAA) using the peroxidase-antiperoxidase technique. The first patient, who had a squamous carcinoma confined to the uterine cervix, was negative for HSV-TAA when tested with rabbit anti-HSV-TAA, but was positive when tested by complement fixation. The second and third patients had tumor extending beyond the cervix but without parametrial involvement. Serologic and immunoenzymatic evaluations showed the second patient to be positive for HSV-TAA and the third patient to be negative. The fourth patient showed obvious parametrial involvement. This patient was positive for HSV-TAA when

tested immunoenzymatically or serologically, but was negative when tested with nonimmune rabbit serum. The fifth patient had adenoacanthoma and lacked antibodies to HSV-TAA. However, sera from all five patients reacted with antigens of HSV types 1 and 2 in the complement-fixation test. The data suggest a role for HSV in certain gynecologic cancers. (12 refs)

- 79-2195 Anatomy of Herpes Simplex Virus DNA. XI. Apparent Clustering of Functions Effecting Rapid Inhibition of Host DNA and Protein Synthesis.** (Eng) Fenwick, M. (Dunn Sch. Pathology, Oxford, England); Morse, L. S.; Roizman, B. *J Virol* 29(2): 825-827; 1979.

The suppression of host protein and DNA synthesis was measured in confluent monolayers of Vero cells infected with herpes simplex virus type 1 (HSV-1), HSV-2, or several intertypic recombinants. The simple technique used is based on the observation that rapid suppression of host synthesis by HSV-2 does not require detectable viral protein or DNA synthesis. Therefore, cells were either (1) infected in the presence of actinomycin D to prevent transcription of viral messenger RNA, and the rate of incorporation of ¹⁴C-amino acids into acid-precipitable material was measured 1.5 hr later; (2) infected with UV light-irradiated virus, and the rate of incorporation of ³H-thymidine was measured 1.5 hr later. The three HSV-2 strains tested inhibited the synthesis of both DNA and protein of the host cell more rapidly than three HSV-1 strains. The HSV-2 strains also caused substantially greater suppression of DNA and protein synthesis than the HSV-1 strains. The two synthesis functions cosegregated in all eight recombinants tested and are therefore controlled by the same gene or by different genes in the same region of the viral DNA. By examining the crossover sites in the DNA's of three recombinants, it was concluded that the gene or genes whose products effect the rapid inhibition of host DNA and protein synthesis lie in the region between 0.52 and 0.59 map units. (9 refs)

- 79-2196 In Vitro Acquisition of Resistance Against Herpes Simplex Virus by Permissive Murine Macrophages.** (Eng) Sethi, K. K. (Institut Medizinische Mikrobiologie und Immunologie, Universitat Bonn, D-5300 Bonn-Venusberg, W. Germany); Brandis, H. *Arch Virol* 59(3): 157-172; 1979.

The ability of peritoneal macrophages (PM) from adult mice to support the productive replication of herpes simplex virus (HSV) types 1 and 2 was studied. PM cultures prepared from adult mice of strains DBA/2J, AKR, and BALB/c supported the replication of infectious HSV-1 and -2. The yield of HSV was significantly higher in cultures of simian virus 40-transformed C57BL/6J PM than in normal PM, and PM from HSV- or Listeria-immunized DBA/2J mice effectively inhibited the replication of test HSV relative to PM from nonim-

mune mice. Supernatant fluids from 72-hr-old mixed lymphocyte cultures (MLC) induced adult DBA/2J and suckling C57BL/6J PM to restrict HSV replication. These macrophages could also inhibit HSV replication if pretreated with the supernatant from cultures of specific-antigen-stimulated HSV- or *Listeria*-immune spleen lymphocytes (SL) or the supernatant from concanavalin A-stimulated SL. Sensitized T cells were essential for the generation of active supernatants. The supernatant from MLC or antigen-stimulated *Listeria*- or HSV-immune SL inhibited mouse, but not hamster or chick, embryo cells. The active factor(s) in the supernatant fluids was not sensitive to heating or exposure to ribonuclease or deoxyribonuclease, but it was inactivated by exposure to hydrochloric acid (pH 2) or trypsin. (34 refs)

- 79-2197 Molecular Genetics of Herpes Simplex Virus. II. Mapping of the Major Viral Glycoproteins and of the Genetic Loci Specifying the Social Behavior of Infected Cells.** (Eng) Ruyechan, W. T. (Dept. Biochemistry, Uniformed Services Univ. Health Sciences, Bethesda, MD, 20014); Morse, L. S.; Knipe, D. M.; Roizman, B. *J Virol* 29(2): 677-697; 1979.

The location in herpes simplex virus (HSV) DNA of the templates specifying the major viral glycoproteins (gp's) and of mutations causing alterations in the social behavior of infected cells, ie, clumping of rounded cells and polykaryocytosis, was mapped. Analysis of HSV-1 x HSV-2 recombinants showed that sequences encoding the gp VP19E map in the S component of the DNA between map units 0.90 and 0.945, whereas sequences encoding the gp's VP8.0, VP7, and VP8.5 are in two locations in the L component of HSV DNA. Apparently, the templates specifying the HSV-1 and HSV-2 gp VP8.0 were not colinear. HSV-1 gp VP8.0 mapped between 0.53 and 0.645 map units, HSV-2 gp VP8.0 between 0.645 and 0.69 map units. The templates specifying gp's VP8.5 and VP7 may be closely linked and colinear in HSV-1 and HSV-2 DNA's; they map between 0.30 and 0.42 map units on the HSV DNA. Marker transfer experiments involving transfection of rabbit skin cells with donor HSV-1 DNA and fragments from several donor strains causing fusion of Vero and/or HEp-2 cells revealed the existence of three *syn* loci specifying the social behavior of cells and one locus (*Cr*) determining the accumulation of gp VP8.0. The *Cr* locus maps to the right of the template specifying gp VP8.0. Loci *syn* 1 and *syn* 2 map at or near the *Cr* locus but can be segregated from it. Locus *syn* 3 maps at or near the template specifying gp's VP7 and VP8.5. The expression of mutations in the *syn* 1 and *syn* 3 loci appears to be cell-type-dependent; the cell-type dependence of the *syn* 2 locus is not clear. (60 refs)

- 79-2198 Polyamine Metabolism in MRC5 Cells Infected with Different Herpesviruses.** (Eng) Tyms, A. S. (Dept. Virology, St. Mary's Hosp. Medical Sch., Paddington, London W2 1PG, England); Scamans, E.; Williamson, J. D. *Biochem Biophys Res Commun* 86(2): 312-318; 1979.

The effect of inhibitors of polyamine metabolism on the replication of herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) and human cytomegalovirus (HCMV) was studied in MRC-5 human diploid fibroblasts. Both methylglyoxal bis(guanyldiazide), an inhibitor of S-adenosyl-L-methionine decarboxylase, and DL- α -methylornithine, an inhibitor of ornithine decarboxylase, were potent inhibitors of the replication of HCMV in MRC-5 cells. These compounds did not affect the replication of HSV-1 or HSV-2. This difference in antiviral effect was related to the stimulation of spermidine and spermine synthesis in host cells following HCMV infection and the inhibition of polyamine metabolism in HSV-1- or HSV-2-infected cells. Inhibition of HCMV replication by the polyamine biosynthesis inhibitors was accompanied by a marked decrease in the formation of intranuclear, DNA-containing inclusions characteristic of HCMV infection. These results suggest that there are significant differences in the replication mechanisms of different herpesviruses. (18 refs)

- 79-2199 Molecular Genetics of Herpes Simplex Virus. III. Fine Mapping of a Genetic Locus Determining Resistance to Phosphonoacetate by Two Methods of Marker Transfer.** (Eng) Knipe, D. M. (Marjorie B. Kovler Viral Oncology Labs., Univ. Chicago, Chicago, IL, 60637); Ruyechan, W. T.; Roizman, B. *J Virol* 29(2): 698-704; 1979.

A genetic locus determining resistance to phosphonoacetic acid (*PAAr*) was transferred from one herpes simplex virus (HSV) genome to another by two methods of marker transfer. In one method, rabbit skin cells were transfected with mixtures consisting of intact DNA extracted from HSV-1 *PAAr* viral capsids and an individual restriction endonuclease DNA fragment generated from HSV-1 *PAAr* DNA. The other method involved transfection of rabbit skin cells with intact HSV-1 *PAAr* DNA and an individual restriction endonuclease fragment generated by digestion of HSV-1 *PAAr* DNA; the mixture had been denatured and reannealed for various periods of time. Both methods yielded viral progeny resistant to PAA. These two methods mapped the *PAAr* locus between positions 0.45 and 0.53 map units on the physical map of the viral DNA. Fine mapping of the *PAAr* locus showed that it maps at or near an *EcoRI* restriction endonuclease site at either 0.46 or 0.49 map units. Using the first method of marker transfer, which depended on recombination in the infected cell between an intact genome and a restriction endonuclease fragment bearing the genetic marker, yields of as much as 10% of the viral progeny bore the marker introduced on the DNA fragment. In the second method, which required repair of a partial heteroduplex formed between intact DNA and a restriction endonuclease fragment bearing the genetic marker, a yield of 35% *PAAr* progeny was achieved using a 1.5-fold excess of fragments. (29 refs)

- 79-2200 Anatomy of Herpes Simplex Virus DNA. XII. Accumulation of Head-to-Tail Concatemers in Nuclei of Infected Cells and Their Role in the Generation of the Four Isomeric Arrangements of Viral DNA.** (Eng) Jacob, R. J. (Marjorie B. Kovler Viral Oncology Lab., Univ. Chicago, Chicago, IL, 60637); Morse, L. S.; Roizman, B. *J Virol* 29(2): 448-457; 1979.

Herpes simplex virus type 1 DNA extracted from virions accumulating in the cytoplasm of infected cells has previously been shown to consist of four populations of linear molecules differing in the orientation of the covalently linked large (L) and small (S) components relative to each other. Together, these four isomeric arrangements of viral DNA display four different termini and four different L-S component junctions. Restriction endonucleases were used to analyze newly replicated viral DNA shortly after the onset of viral DNA synthesis, progeny DNA accumulating in the nuclei late in infection, and rapidly sedimenting DNA present in nuclei of infected cells at 8 hr after infection. In each instance, the nuclear viral DNA contained a decreased concentration of all four terminal fragments and an increased concentration of fragments spanning the junction of L and S components relative to the concentration of other DNA fragments. The results are consistent with the hypothesis that the viral DNA accumulating in the nuclei consists of head-to-tail concatemers arising from the replication of DNA by a rolling-circle mechanism. A model is presented for the generation of all four isomeric arrangements of herpes simplex virus DNA from one arrangement based on excision and repair of unit length DNA from head-to-tail concatemers and on known features of the sequence arrangement of viral DNA. (29 refs)

- 79-2201 Infection of Avian Lymphoblastoid Cell Lines with Type 2 Herpes Simplex Virus.** (Eng) Nii, S. (Dept. Virology, Okayama Univ. Medical Sch., Shikatacho, Okayama 700, Japan); Arita, K.; Asai, T. *Biken J* 21(3): 115-119; 1978.

The susceptibility of the avian lymphoblastoid cell lines 1104 X-5 and MSB-1 to infection with herpes simplex virus type 2 (HSV-2) was examined by electron microscopy and by the fluorescent antibody technique. MSB-1 cells were infected at an input multiplicity of 4 and 1104 X-5 cells at a multiplicity of 5. At 32 hr after infection, herpes-type virus particles could be seen in a few 1104 X-5 cells. Extracellular particles of HSV occasionally coexisted with C-type particles. At 15 hr after infection, approx 2%-3% of MSB-1 cells contained herpes-type virus. Most virus-infected nuclei contained capsids with a low-density core that was 40 nanometers in diameter. Microtubules, which are characteristic of HSV infection, were also seen in the nuclei of HSV-2 infected MSB-1 cells. In fluorescent antibody studies, the antigen began to appear 4 hr after infection, and the percentage of antigen-positive cells increased as infection proceeded. However, the max percentage reached was 20% in 1104 X-5 cells at 9 hr and 9% in MSB-1 cells at 10 hr. These results indicate that the two

avian lymphoblastoid cell lines are fairly susceptible to a human herpesvirus, but it is not known why most cells of both lines were so resistant to HSV-2 infection even when exposed to a high dose of the virus. (9 refs)

- 79-2202 Enhancement of Biochemical Transformation of Mammalian Cells by Herpes Simplex Virus Following Nitrosomethylurea Treatment.** (Eng) Howett, M. K. (Dept. Microbiology, Milton S. Hershey Medical Center, Hershey, PA, 17033); Pegg, A. E.; Rapp, F. *Cancer Res* 39(3): 1041-1045; 1979.

A quantitative assay for the biochemical transformation of thymidine kinase-deficient mouse cells (N cIA cl10) to an enzyme-positive phenotype by herpes simplex virus type 2 (HSV) was used to study the effects of a noncytotoxic concentration (0.04 mM) of nitrosomethylurea (NMU) on cell transformation. Transformation was enhanced in cells treated with NMU 24 hr after exposure to HSV compared with untreated virus-exposed cells. The enhancement in susceptibility to transformation disappeared when 72 hr elapsed between virus exposure and NMU treatment. By 72 hr after infection, > 90% of the 7-methylguanine and more than 75% of the O⁶-methylguanine were removed from the cell DNA. At 24 hr postinfection, however, less of the damage had been repaired, and enzymatic excision and repair were actively occurring. Thus, enhanced susceptibility to transformation coincided with the presence of alkylated bases and/or ongoing repair. HSV infection did not alter the ability of the cells to repair NMU damage. (41 refs)

- 79-2203 Transfer of the Herpes Simplex Thymidine Kinase Gene from Human Cells to Mouse Cells by Means of Metaphase Chromosomes.** (Eng) Sabourin, D. J. (Div. Human Genetics, Children's Hosp. Medical Center, Harvard Medical Sch., Boston, MA, 02115); Davidson, R. L. *Somatic Cell Genet* 5(2): 159-174; 1979.

To test for the integration of the herpes simplex virus (HSV) thymidine kinase (TK) gene into the chromosomes of HSV-transformed human cells, the latter were isolated following exposure of TK-deficient human cells to UV-inactivated HSV type 1 and selection in HAT medium. The transformed human cells produced TK with the electrophoretic characteristics of the activity appearing in cells lytically infected with HSV-1. Next, metaphase chromosomes were purified from the transformed human cells and incubated with TK-deficient mouse cells. Several presumptive herpes gene transferents of independent origin were isolated, and three were characterized in detail. All three lines expressed herpes TK activity rather than mouse or human TK. The gene transferents contained no intact human chromosomes. When removed from selective pressure, they rapidly lost the TK⁺ phenotype. However, upon continued growth in nonselective medium, a subpopulation in which the TK⁺ pheno-

type had become more stabilized appeared. The results indicate that the herpes TK gene was integrated into the genome of the HSV-transformed human cells and that its transfer to the TK-deficient mouse cells was mediated by metaphase chromosomes. (32 refs)

- 79-2204 Replication of Herpes Simplex Virus Type 2 in Normal Dysplastic and Neoplastic Human Cervical Epithelia.** (Eng) Mandeville, R. (Institut du Cancer de Montreal, Centre Hospitalier Notre Dame, 1560 Sherbrooke est, Montreal, Canada H2L 4M1); Holloway, A.; Laughlan, S. C.; Simard, R. *Eur J Cancer* 5(3): 351-361; 1979.

The organ culture method was used to determine the response of cultured human cervical epithelium explants to herpes simplex type 2 (HSV-2) infection. Biopsied cervical epithelium from 30 patients with cervical dysplasia, 15 with cervical carcinoma in situ (CIS), 20 with cervical invasive cancer, and 185 normal subjects was used. The cultured cells resembled their in vivo counterparts morphologically. As shown by (³H)-thymidine labeling, proliferative cells were confined to the parabasal and basal layers of the squamous epithelium in the normal preparations. In the dysplastic and neoplastic tissues, labeling of cells in the superficial zone reflected disturbances in the rate of DNA replication. Within 4 days after HSV-2 infection, 70% of the epithelial cells from the normal preparations showed cytopathological changes characteristic of virus transformation. The explants derived from cervical dysplasias showed the same changes in response to HSV-2 infection, but they showed them 1 to 2 days earlier than the normal tissues. The CIS and invasive cancer explants responded in an identical manner, but they also showed the presence of large numbers of polykaryocytes postinfection that were not present in the transformed dysplastic or normal preparations. Virus particles were found in all infected explants 72 hr postinfection, and the virus titer remained high at 96 hr postinfection, reaching values of 9.5×10^1 plaque-forming units/ml. The amount of infective virus always decreased significantly later in the course of infection. (24 refs)

- 79-2205 Uninhibited Growth and Metastases of Herpes Simplex Virus-Transformed Cells in Virus-sensitized Hosts.** (Eng) Hay, K. A. (Dept. Microbiology and Specialized Cancer Res. Center, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033); Lausch, R. N. *Int J Cancer* 23(3): 337-343; 1979.

Four established lines of hamster cells transformed by herpes simplex virus type 1 or 2 (HSV-1 and HSV-2) that were not shedding the virus were examined for continued expression of virus-associated antigens. Sera collected from hamsters bearing HSV isografts showed a generally low incidence of neutralizing activity against HSV-1 and HSV-2, suggesting that only small quantities of virion antigen were present in

the cells. Hyperimmunization studies in rabbits supported this explanation. Repeated immunization of rabbits with tumor cells in Freund's complete adjuvant resulted in the production of specific virus-neutralizing antibody. Hamsters sensitized to HSV and resistant to virulent virus challenge did not reject low numbers of tumor cells, and the incidence of lung metastases was not significantly reduced. Cervical lymph node cells from hamsters immunized with HSV-1 were significantly cytotoxic for virus-infected hamster embryo fibroblasts, but they did not lyse any of the HSV-1- or HSV-2-transformed cell lines tested. Studies with tumor cell-sensitized hamsters indicated that the HSV-transformed lines were at most only weakly immunogenic and/or immunosensitive in syngeneic hosts. Animals immunized with HSV-1 plus HSV-1-transformed tumor cells were as resistant to tumor cell challenge as hosts immunized to tumor cells only. The data indicate that the HSV tumor lines expressed low levels of virus structural antigens but not virus-specific transplantation-rejection antigen. (25 refs)

- 79-2206 Proliferation of Hamster Embryo Fibroblast Cultures Infected with Herpes Simplex Virus.**

(Rus) Ageenko, A. I. (Lab. Virology, P. A. Hertsen Res. Oncological Inst., Moscow, USSR); Kogan, I. Ia. *Vopr Onkol* 25(2): 39-42; 1979.

To determine whether human herpes simplex virus type 2 can stimulate DNA synthesis in both permissive and nonpermissive systems, hamster embryo fibroblast (HEF) cultures were infected with the virus prior to monolayer formation and then incubated in medium containing ³H-thymidine. The labeling index started to increase within the first hours of infection, and it reached a max after approx 15 hr. At 72 hr, the labeling index was 8%, compared with 2% in control cultures. Infection of HEF during the stationary phase also increased proliferative activity: 72 hr after infection, the labeling index was 5%-6%, compared with 1%-2% in control cultures. (9 refs)

- 79-2207 Transformation of Hamster Embryonic Fibroblast Cells by UV-Irradiated Human Cytomegalovirus.** (Eng) Boldogh, I. (Inst. Microbiology, Univ. Medical Sch., H-4012 Debrecen, P.O.B. 17, Hungary);

Gonczol, E.; Vaczi, L. *Acta Microbiol Acad Sci Hung* 25(4): 269-275; 1978.

The transformation of Syrian hamster embryo (HEF) cells by human cytomegalovirus (HCMV) was studied. Nineteen to 24 days after inoculation of HEF with partially UV-inactivated HCMV at approx 1 plaque-forming unit/cell, rapidly multiplying foci of cells with altered morphology appeared. Only one (87-TRH-5) of 11 such foci remained capable of multiplying after isolation. This clone consisted of fibroblast-like cells with large, sometimes multiple, nuclei. Three cell lines derived from 87-TRH-5 showed a fibroepithelioid morphology with occasional multinuclear giant cells. Newborn

and weanling hamsters inoculated with 10^7 - 10^8 87-TRH-5 cells developed fibrosarcomas, as did weanling hamsters inoculated with cell lines derived from the tumors. The oncogenicity of the derivative cell lines was greater than that of the parental line. The transformed cells showed HCMV-specific cytoplasmic and surface antigen, but attempts to isolate infectious virus and to detect HCMV-specific nuclear antigens(s) failed. (14 refs)

79-2208 Size of the Intracellular Circular Epstein-Barr Virus DNA Molecules in Infectious Mononucleosis-derived Human Lymphoid Cell Lines. (Eng) Adams, A. (Dept. Medical Microbiology, Univ. Goteborg, Goteborg, Sweden); Bjursell, G.; Gussander, E.; Kolias, S.; Falk, L.; Lindahl, T. *J Virol* 29(2): 815-817; 1979.

The size of the nonintegrated circular Epstein-Barr virus (EBV) DNA molecules isolated from seven different human lymphoblastoid cell lines of infectious mononucleosis origin was determined by sedimentation analysis and by direct contour length measurements on electron micrographs. All cell lines investigated contained 10-40 EBV genome equivalents per cell, as estimated by hybridization with EBV complementary RNA. Six lines had intracellular circular EBV genomes of the same size as linear virion DNA molecules. The seventh line, established with the B95-8 strain of EBV, was the only one found to have circular EBV DNA molecules significantly smaller than virion DNA. The data show that intracellular EBV DNA circles of reduced size do not generally occur in infectious mononucleosis-derived cell lines. (12 refs)

79-2209 Establishment of a Malignant, Epstein-Barr-Virus (EBV)-negative Cell-Line from the Pleural Effusion of a Patient with Hodgkin's Disease. (Eng) Schaadt, M. (Abteilung fur Hamatologie/Onkologie, Medizinische Hochschule Hannover, D-3000 Hannover, W. Germany); Fonatsch, C.; Kirchner, H.; Diehl, V. *Blut* 38(2): 185-190; 1979.

A malignant in vitro cell line (L 428) established from the pleural effusion of a 37-yr-old woman with Hodgkin's disease (HD: nodular sclerosing type, Stage IVB) is described. The culture grew as a single cell suspension with a doubling time of 42-46 hr and a max concentration of 1.56×10^6 cells/ml. Besides large (50-80 μ m) multinuclear cells with smooth membrane surfaces or bearing a few short curled villi, medium-sized (30-50 μ m) mono- or binuclear cells with hairlike membrane protrusions and small (15-30 μ m) mononuclear cells could be identified. The cells were PAS- and acid phosphatase-positive. They showed neither B-cell nor T-cell properties; Fc receptors were present in 7% of the cells. Phagocytosis and lysozyme production could not be detected. The line did not exhibit Epstein-Barr virus-specific antigens (nuclear antigen and virus capsid antigen). According to cytogenetic studies performed immediately after the line was

established, the cells had an aneuploid karyotype with various chromosomal aberrations. The identity of eight marker chromosomes indicated that the line had a clonal origin. Intracranial heterotransplantation of cells into two nude mice resulted in tumor formation in both. Literature reports of in vitro-cultivated HD-derived cell lines are conflicting, which might be due to the fact that different cell systems (B or T lymphocytes and/or macrophages-histiocytes) might be transformed by the initiating malignant process followed by the evolution of multiple clinical features known collectively as HD. (17 refs)

79-2210 Epstein-Barr Virus RNA in Burkitt Tumor Tissue. (Eng) Dambaugh, T. (Section Infectious Disease, Dept. Medicine, Committee Virology, Kourer Viral Oncology Labs. Univ. Chicago, 910 E. 58th St., Chicago, IL, 60637); Nkrumah, F. K.; Biggar, R. J.; Kieff, E. *Cell* 16(2): 313-322; 1979.

Analysis of the viral RNA in four Burkitt's lymphoma (BL) biopsies indicated that the tumor tissue contained RNA homologous to at least 3%-6% of the DNA of Epstein-Barr virus (EBV). Most of these RNA species accumulated in the polyadenylated RNA fraction of the BL tissue. Two approaches were used to determine the location within the EBV genome of the DNA sequences that encode stable RNA in two BL biopsies, F and S, which contained 6-10 copies per cell of at least 80% of the EBV genome. With the first approach, 32 P-EBV DNA homologous to polyadenylated or nonpolyadenylated RNA's from the F, S, or R tumors was hybridized to blots of fragments of EBV DNA. With the second approach, polyadenylated or nonpolyadenylated RNA's from the F or S tumors were hybridized to separated, labeled fragments of EBV DNA in soln. The results indicated that (1) most of the viral RNA in BL tissue is encoded by approx 20% of the Hsu I D fragment, 20% of the Eco RI A/Hsu I A double-cut fragment, and 3% of the Hsu I B fragment of EBV DNA; (2) an abundant RNA species in tumor tissue is homologous to the "additional DNA" present in the W91 and Jijoye/HR-I BL isolates of EBV and absent in the B95-8 virus, an isolate of EBV from outside the Burkitt endemic region; and (3) there is little or no homology to other regions of the EBV genome. (41 refs)

79-2211 Nucleosomal Structure of Epstein-Barr Virus DNA in Transformed Cell Lines. (Eng) Shaw, J. E. (Cancer Res. Center, Dept. Microbiology and Immunology, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514); Levinger, L. F.; Carter, C. W. *J Virol* 29(2): 657-665; 1979.

Micrococcal nuclease digestion was used to analyze the Epstein-Barr virus (EBV) DNA structure in nuclei of B-lymphoblastoid cell lines established from human lymphomas. Digests of virus-producing (P3HR-1), non-virus-producing

(Raji), and superinfected Raji cell nuclei were fractionated by electrophoresis on agarose gels, transferred to nitrocellulose, and hybridized to ³²P-labeled EBV DNA. The viral DNA of Raji nuclei produced a series of bands on electrophoresis whose lengths were integral multiples of a unit size that was the same as the repeat length of host DNA. Viral DNA in nuclei of P3HR-1 and superinfected Raji cells produced faintly visible bands superimposed on a smear of viral DNA that dominated the hybridization pattern. No differences were detected in the patterns when total DNA digests from Raji, P3HR-1, and an EBV DNA-negative lymphoma cell line (U-698M) were analyzed by ethidium bromide staining or by hybridization with the use of ³²P-labeled lymphoblastoid cell DNA as a probe. It is concluded that the EBV episomal DNA of Raji cells is folded into nucleosomes, whereas most of the viral DNA of P3HR-1 and superinfected Raji cells is not. This pattern of DNA organization differs significantly from that in papova viruses. (57 refs)

79-2212 [¹²⁵I] C1q-Binding Activity and Its Relationship with Anti-Epstein-Barr Virus Antibodies in Sera from Nasopharyngeal Carcinoma Patients. (Eng) Lameilin, J. P. (Unit Biological Carcinogenesis, Internatl. Agency Res. on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France); Vincent, C.; Souissi, T.; Revillard, J. P. *Eur J Cancer* 15(2): 163-171; 1979.

¹²⁵I-labeled complement component C1q-binding activity (C1q-BA) and antibody titers against Epstein-Barr (EB) viral capsid antigen (VCA), nuclear antigen (EBNA), and early antigen (EA) were determined in sera from 28 nasopharyngeal carcinoma patients (NPC) and 66 matched controls from Tunisia. C1q-BA increased with age, but did not show a significant association with stage of NPC. Significantly more sera were positive for C1q-BA among the NPC patients than among the controls. The mean titers of IgG anti-VCA and anti-EBNA antibodies and the proportion of anti-EA-positive sera were also significantly higher among the NPC patients than among the controls. The anti-VCA titers in the NPC sera increased with age for both IgG and IgA classes. IgG anti-VCA, but not IgA anti-VCA, anti-EA, or anti-EBNA, was positively correlated with the percentage of bound C1q. (34 refs)

79-2213 Superinfection of EBV-Carrying Lines with Herpes Virus Papio (HVP): Induction of Early Antigen (EA) and Inhibition of Cellular DNA Synthesis. (Eng) Steinitz, M. (Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden); Klein, G. *Eur J Cancer* 15(2): 217-222; 1979.

A possible correlation between the ability to induce early antigen and the ability to inhibit DNA synthesis was studied using an Epstein-Barr virus (EBV)-related herpesvirus [*H. papio* (HVP)] derived from the baboon virus-producer lym-

phoid cell line 9B. For comparison, the P3HR-1 variant of EBV was also studied. Both 9B and P3HR-1 viruses inhibited the DNA-stimulating effect of EBV variant B95-8 and of the B-cell mitogen *Staphylococcus aureus* on human lymphocytes, but neither inhibited DNA stimulation by the T-cell mitogen phytohemagglutinin. 9B and P3HR-1 viruses also inhibited DNA metabolism in EBV-receptor-positive cells. Pretreatment of either virus with EBV-neutralizing Burkitt's lymphoma serum abolished this inhibitory activity. The inhibiting effect was not due to residual viral genome, and the inhibition was manifested only in cells with a functionally active EBV receptor. The inability of the two viruses to immortalize normal cells and their ability to induce EA in certain cells may be related to their inhibitory effect on DNA synthesis. (24 refs)

79-2214 Physical Characterization of the Deoxyribonucleic Acids of Different Human Papilloma Viruses (HPV). (Eng) Gissmann, L. (Institut fur Virologie, Zentrum fur Hygiene, Hermann-Herder-Strasse 11, D-7800 Freiburg, W. Germany); zur Hausen, H. *Med Microbiol Immunol (Berl)* 166(1/4): 3-11; 1978.

The mol wt, buoyant density, sedimentation behavior, and cross homology of DNA from human papilloma viruses (HPV) 1, 2, and 3 were determined. HPV 1, 2, and 3 DNA appeared to be indistinguishable as far as mol wt (4.9×10^6 daltons), buoyant density (1.700 μ /ml), sedimentation values of the three circular DNA components (Co I: 22S-23S, Co II: 17S; and Co III: 16S), and homology are concerned. HPV 4 DNA, which is entirely different from HPV 1, 2, and 3 in its restriction enzyme pattern, did not hybridize with complementary RNA (cRNA) transcribed in vitro from HPV 1 DNA. The cRNA represented the entire viral genome. Therefore, the negative hybridization with HPV 4 DNA indicates that no base homology exists in any region of the two genomes. (16 refs)

79-2215 Characteristics of the Lesions and Risk of Malignant Conversion Associated with the Type of Human Papillomavirus Involved in Epidermodysplasia Verruciformis. (Eng) Orth, G. (Unite de Recherche sur l'Etiologie Virale des Cancers Humains, LA 147 CNRS, U 140 INSERM, Institut Gustave-Roussy, 94800 Villejuif, France); Jablonska, S.; Jarzabek-Chorzelska, M.; Obalek, S.; Rzeska, G.; Favre, M.; Croissant, O. *Cancer Res* 39(3): 1074-1082; 1979.

Fourteen epidermodysplasia verruciformis (EV) patients were studied to correlate the type of human papillomavirus (HPV) found in benign lesions to the clinical aspects and to the course of the disease; 9 patients were familial cases, and 6 had cancer. The type of HPV was determined by RNA-DNA filter hybridization, using complementary RNA's transcribed from the DNA's of the four types of HPV

previously identified, and by immunofluorescence studies using antisera specific for the four virus types. HPV-3 was found in seven patients presenting lesions of only the verruca plana type. These cases were mostly stationary or abortive and showed no malignant conversion. HPV-4 was detected in four patients with lesions of different types: very flat, often reddish warts; reddish plaques; and pityriasis versicolor-like pigmented or achromic plaques. All these patients showed cancers. Both types of viruses were found in two patients: HPV-3 in flat wartlike lesions and, for one patient, in large confluent pigmented plaques; and HPV-4 in reddish or pityriasis versicolor-like plaques. One of these patients had early malignant lesions (Bowen's disease) and the other had multiple carcinomas. For one patient, the type of virus could not be identified because of an insufficient amount of material. These results point to the role of virus in the pathogenesis of EV, together with genetic and immunological factors. They suggest, in addition, different oncogenic potentials for viruses involved in the disease. (29 refs)

- 79-2216 Characterization of Proteins of Human Papilloma Viruses (HPV) and Antibody Response to HPV 1.** (Eng) Pfister, H. (Institut für Virologie, Zentrum für Hygiene, Hermann-Herder-Strasse 11, D-7800 Freiburg, W. Germany); zur Hausen, H. *Med Microbiol Immunol (Berl)* 166(1/4): 13-19; 1978.

Human papilloma virus (HPV) isolates from 300 wart biopsies were characterized as HPV 1 and HPV 4 by a complement-fixation assay with specific rabbit antisera. The isolates from 30% of the biopsies were HPV 1 and 14% were HPV 4. Virus preparations from 2% did not react with either of the two antisera, and no virus could be isolated from 54% of the biopsies. An examination of the HPV 1 proteins indicated that the major structural proteins VP2 and VP3 are trypsin-sensitive. Tryptic degradation gave distinct polypeptides with mol wts of 23,000-37,000, that may be correlated to minor protein components of HPV 1 preparations. HPV 1 histonelike proteins, which comigrated with purified cellular histones upon sodium dodecyl sulfate gel electrophoresis, were analyzed in an acetic acid-urea system. The H3- and H4-like proteins differed from the cellular histones. It is not known whether this is due to modification by acetylation, as described for polyoma viruses (histone modification in these viruses appears to be correlated with oncogenicity). In a non-selected population, most children are free of HPV 1 antibodies until they are 5 yr old. Between 5 and 15 yr, about 50% of the population has HPV 1 antibody-positive serum. Serum from a patient with epidermodysplasia verruciformis, which has a tendency to malignant conversion, reacted only with HPV 4 particles when tested by immunoelectron microscopy. However, HPV 1 antibodies could be demonstrated at a titer of 1/10 by radioimmunoassay. Whether HPV 4 is causally connected with epidermodysplasia remains to be established. (11 refs)

- 79-2217 Molecular Cloning of Polyoma Virus DNA in *Escherichia coli*: Plasmid Vector System.** (Eng) Israel, M. A. (DNA Recombinant Res. Unit, Natl. Inst. Allergy and Infectious Diseases, Bethesda, MD, 20014); Chan, H. W.; Rowe, W. P.; Martin, M. A. *Science* 203(4383): 883-887; 1979.

Studies were carried out to characterize and evaluate the safety of a plasmid vector system for recombinant DNA research. In this system, *Escherichia coli* carry a recombinant plasmid that contains the entire polyoma virus genome. Insertion of the PY genome into the plasmid vector pBR322-*E. coli* χ 1776 at the restriction endonuclease *Eco*RI site leaves the entire late region of the viral genome intact, but insertion at the *Bam*HI site leaves the entire early region intact. Experiments confirmed that the entire PY genome was present in the pBR322-*E. coli* χ 1776 system. The orientation of the PY DNA insert in the recombinant plasmid molecule was ascertained by digestion with *Hind*III. Further experiments confirmed that viral-specific RNA was synthesized in bacterial minicells containing recombinant PY-pBR322 plasmids. The results of the mouse antibody production test showed that recombinant plasmids were unable to initiate productive PY infections in mice and that no free PY DNA I was present in the bacterial cells. When purified recombinant DNA preparations were first cleaved with the same restriction enzyme as was used in their construction, nearly all injected animals developed PY infection. This indicates that PY DNA, when combined with pBR322, is replicated with sufficient fidelity in *E. coli* to preserve the numerous functions required for productive infection. Even when administered to mice as massive doses of bacteria, none of the four *E. coli* χ 1776 preparations containing recombinant plasmids resulted in a PY infection after ip or sc injection, nor did they induce infection when fed repeatedly to animals for total doses of 0.4-1.0 μ g PY DNA. (25 refs)

- 79-2218 Nucleotide Sequence of the BK Virus DNA Segment Encoding Small t Antigen.** (Eng) Dhar, R. (Lab. Molecular Virology, NCI, NIH, Bethesda, MD, 20014); Seif, I.; Khoury, G. *Proc Natl Acad Sci USA* 76(2): 565-569; 1979.

The nucleotide sequence from 0.64 to 0.53 map units of the BK virus genome coding for the small tumor (t) antigen was determined. There is only one open reading frame that can code for a polypeptide of 172 amino acids, the putative small t protein. Beyond this segment, multiple termination codons are present in all three reading frames. There is considerable nucleotide and amino acid sequence homology between this region of BK virus and the analogous region of simian virus 40, especially in the proximal portion from 0.64 to 0.60 map units, which is most likely common to the small t and large T BK virus proteins. A comparison of the conserved sequences within the early papovavirus genes both confirms the evolutionary relationship between these viruses and gives an idea of the amino acid composition of the regions required

for T-antigen functions. (29 refs)

- 79-2219 Multiple 5' Terminal Cap Structures in Late Polyoma Virus RNA.** (Eng) Flavell, A. J. (Imperial Cancer Res. Fund Labs., P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England); Cowie, A.; Legon, S.; Kamen, R. *Cell* 16(2): 357-371; 1979.

The 5'-terminal capped structures present on late polyoma (Py) virus messenger RNA's (mRNA's) were characterized and mapped. Nuclear and cytoplasmic Py virus-specific RNA extracted from ³²P-labeled mouse embryo cells late during productive viral infection was analyzed for the presence of 5'-terminal capped structures by complete digestion with RNases T1, T2, and A, followed by two-dimensional electrophoretic fractionation. Seven major cap I structures (m⁷GpppNm¹pN²p) were observed in both cases. These termini were further characterized by digestion with penicillium nuclease P1, followed by product analysis in a variety of alternative separate systems. Each structure had an individual combination of N¹ and N² nucleotides in which N¹ was always a purine nucleotide but N² was any nucleotide subject to the single exception that m⁷GpppGmpCp is found only in low yield. Four different cap II derivatives (m⁷GpppNm¹pNm²pN³p) of four of the cap I structures were also detected in cytoplasmic RNA. None of the termini described were derived from contaminating host cell RNA. All of these cap structures mapped on the Py viral DNA genome between 66 and 71 map units, a region distant from the 5' end of the bodies of two of the three late Py mRNA's. All the Py virus-specific cap structures, however, were present in each of the purified 16S, 18S, and 19S late mRNA's. These data suggest that families of capped leader sequences of varying sizes are attached to the main body of each late Py mRNA species by a splicing mechanism. (44 refs)

- 79-2220 Amplification in the Leader Sequence of Late Polyoma Virus mRNAs.** (Eng) Legon, S. (Imperial Cancer Res. Fund Labs., P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England); Flavell, A. J.; Cowie, A.; Kamen, R. *Cell* 16(2): 373-388; 1979.

Ribonuclease T1 fingerprints of the three "late" polyoma virus messenger RNA's (mRNA's) showed that oligonucleotides of the leader sequence are present in multiple copies in each mRNA. These oligonucleotides, however, appeared to be unimolar in fingerprints of complete, continuous transcripts of the late strand of the viral DNA. Oligonucleotides that are represented only once in the DNA are thus reiterated in the mature mRNA's. Consequently, when mRNA was hybridized to the leader region of immobilized viral DNA, those copies present in excess of their genomic representation failed to hybridize and were released by RNase treatment. Analysis of the RNase-resistant hybrids revealed a series of leader species with complex sequence arrangements. It is suggested

that these complicated reiterated sequences are generated during the processing of a precursor RNA that extends several times around the genome. This RNA would be shortened by a series of splicing reactions that conserve sequences from the leader region and attach them to a suitable coding sequence. (35 refs)

- 79-2221 Molecular Cloning of Polyoma Virus DNA in *Escherichia coli*: Lambda Phage Vector System.** (Eng) Chan, H. W. (DNA Recombinant Res. Unit, Natl. Inst. Allergy and Infectious Diseases, Bethesda, MD, 20014); Israel, M. A.; Garon, C. F.; Rowe, W. P.; Martin, M. A. *Science* 203(4383): 887-892; 1979.

The molecular cloning of recombinants formed between the *Escherichia coli* EK2 lambda phage vector λgtWES.λB DNA and polyoma (PY) DNA and an evaluation of the infectivity of the recombinant plasmids in mouse cells in vivo and in vitro are described. The PY genome can be inserted into the lambda vector DNA in either of two orientations at the *Eco* RI site, and cleavage of the recombinant DNA preparations with *Bam*HI permitted the unambiguous mapping of the viral DNA inserts. The recombinant phages contained a monomeric or a dimeric insert. The tandem insertion of more than one copy of DNA into the λgtWES.λB vector resulted in unstable recombinants that shed extra copies of the inserts at a high frequency. Recombinant preparations containing a single copy of DNA failed to induce PY infection when inoculated parenterally in weanling mice or when tested in cultured mouse embryo cells. PY infection did occur in 2/5 mice inoculated sc with 2.8 μg of recombinant phage containing the dimeric insert (phage D) and in 2/5 inoculated with 23 μg of DNA prepared from *E. coli* infected with phage D. Injection of live *E. coli* infected with phage D failed to induce infection in any of 28 mice. Feeding of comparable infected bacteria did not induce PY infection in any of 13 mice tested. The authors conclude that in most experimental systems, tandem inserts are highly unlikely to occur. The results are highly reassuring with respect to the safety of cloning viral genomes in *E. coli*. (10 refs)

- 79-2222 Polyoma Virion and Capsid Crystal Structures.** (Eng) Adolph, K. W. (Dept. Biochemistry, Univ. Minnesota Medical Center, Minneapolis, MN, 55414); Caspar, D. L.; Hollingshead, C. J.; Lattman, E. E.; Phillips, W. C.; Murakami, W. T. *Science* 203(4385): 1117-1120; 1979.

Sodium sulfate was used to obtain large single crystals of polyoma virions and capsids suitable for x-ray structure analysis. The particles in the crystals were arranged on a body-centered cubic lattice. The small-angle x-ray reflections from the well-ordered virion crystals were weak, whereas those from the capsid crystals and from the virion crystals with comparable short-range disorder were relatively strong. The differences probably resulted, at least in part, from the

scattering contribution of the viral chromatin core. By electron microscopy (EM), the capsids appeared hollow and the virions had a solid core. Vacancies were characteristic of the crystals, especially the capsids, and they gave the sections a moth-eaten appearance. There was a close correlation between virus structure information obtained by x-ray diffraction and that obtained by EM. The bumps in the capsid surface revealed by EM were the dominant feature determining the intensity of the diffraction to a resolution of about 30 Å. The structure and variability of the viral chromatin core can then be analyzed by comparison of electron-density maps. (22 refs)

79-2223 State and Organization of Polyoma Virus DNA Sequences in Transformed Rat Cell Lines. (Eng)

Birg, F. (U. 119, Institut National de la Sante et de la Recherche Medicale, 13009 Marseille, France); Dulbecco, R.; Fried, M.; Kamen, R. *J Virol* 29(2): 633-648; 1979.

Restriction endonuclease digestion was used to analyze the polyoma (PY) DNA sequences present in tumor (T)-antigen-positive transformed rat cell lines isolated by growth in soft agar. The transformed lines were isolated as colonies growing in agar after infection of F2408 rat cells with low multiplicities of wild-type virus. Viral DNA present in the transformed cells was analyzed by fractionation of the cellular DNA on agarose gels before and after digestion with various restriction endonucleases, transfer of the DNA onto a sheet of nitrocellulose, and subsequent autoradiographic detection of the bands containing viral sequences by annealing the resulting blots to in vitro-labeled ³²P-Py DNA. Less than one copy of viral DNA per diploid equivalent of cellular DNA can be detected with this procedure. Five lines, independently derived, were studied in detail. All five lines, when examined after a minimum number of passages in culture, contained both free and apparently integrated viral DNA. The free PY DNA in three of the lines was indistinguishable, by restriction enzyme analysis, from wild-type viral DNA, whereas the two other lines also contained smaller free DNA molecules that lacked parts of the wild-type genome. The integrated DNA in the five lines existed as head-to-tail tandem repeats of unit-length Py DNA covalently attached to nonviral DNA. The same five Py-transformed rat lines were examined after further passages in culture. Free viral DNA was then either undetectable or greatly reduced in amount, whereas the high-mol-wt, integrated units persisted after passage of the cells. Ten subclones, derived from one of the five lines selected for detailed analysis, showed some variations in the quantity and size of the free viral DNA as well as minor alterations in the pattern of the apparently integrated sequences. (64 refs)

79-2224 Transformation of Human Embryonic Kidney Cells by Human Papovavirus BK. (Eng)

Purchio, A. F. (Molecular Biology Inst., Univ. California at

Los Angeles, Los Angeles, CA, 90024); Fareed, G. C. *J Virol* 29(2): 763-769; 1979.

The interaction of human papovavirus BK (BKV) with secondary human embryonic kidney (HEK) cells was investigated to define how the virus exists within its natural host. Infection of HEK cells with BKV at a multiplicity of 10 resulted in cellular lysis and degeneration within 7 days. After 30 days, multilayered colonies of transformed cells appeared; these cells were subcultured for analyses. The BK-HEK cells uniformly expressed BKV tumor (T) antigen but were only 1% V-antigen positive. They produced infectious virus and were resistant to superinfection by BKV. They reached a saturation density of 1.3×10^5 cells/cm² in medium with 5% fetal calf serum, were able to grow in medium containing 2% serum, and did not form colonies in soft agar or tumors in nude mice. Nonintegrated, superhelical BKV DNA was detected in the noncloned cells as expected, because they were persistently infected and contained RNA transcripts complementary to both early and late regions of the BKV genome. Analysis of T-antigen-positive clonal isolates of the BK-HEK cells with restriction endonucleases revealed an absence of free viral DNA and the presence of integrated BKV DNA sequences corresponding to the early region of the BKV genome. These studies demonstrate the stable transformation of human cells by BKV. However, the transformed human cells that retain and express part of the BKV genome do not fully manifest the growth properties of other papovavirus-transformed cells. (31 refs)

79-2225 Nucleotide Sequence Analysis of Two Simian Virus 40 Mutants with Deletions in the Late Region of the Genome. (Eng)

Contreras, R. (Lab. Molecular Biology, State Univ. Ghent, B-9000 Ghent, Belgium); Cole, C.; Berg, P.; Fiers, W. *J Virol* 29(2): 789-793; 1979.

Two mutants of simian virus 40, *dl*-1261 and *dl*-1262, have deletions that map between coordinates 0.90 and 0.95. Both affect the structure of the two minor virion proteins VP2 and VP3. The precise location and size of the deletions were determined by nucleotide sequence analysis. Nucleotides deleted from the two mutants were defined by digesting the mutant DNA with *AtuI* and labeling the 5' ends of the resulting fragments with [γ -³²P]ATP and T₄ polynucleotide kinase. Restriction endonuclease *HaeIII* was used for the second digestion to separate the labeled ends of the fragments. Mutant *dl*-1261 had a deletion of 54 base pairs, was temperature-sensitive for the protein defined by the D complementation group, and promoted the synthesis of shorter VP2 and VP3 polypeptides. Mutant *dl*-1262 was viable irrespective of temperature and had a deletion of 36 base pairs, 23 of which overlapped the deletion in *dl*-1261. Since these mutants produce normal VP1, the deleted regions probably have no function in the splicing of precursor RNA to the VP1 messenger RNA. (16 refs)

- 79-2226 Rapid Sequence Determination of Late Simian Virus 40 16S mRNA Leader by Using Inhibitors of Reverse Transcriptase.** (Eng) Bina-Stein, M. (Lab. Biology Viruses, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20014); Thoren, M.; Salzman, N.; Thompson, J. A. *Proc Natl Acad Sci USA* 76(2): 731-735; 1979.

The problem of sequencing desired regions of selected messenger RNA's (mRNA's) was approached by using given DNA restriction fragments, which anneal to the mRNA at specific regions, as primers for the reverse transcriptase (RNA-dependent DNA polymerase) reaction. Addition of 2', 3'-dideoxynucleoside triphosphates as chain terminators during the reverse transcriptase reaction allows rapid sequence determination of the complementary DNA. This method was used to study the major late cytoplasmic 16S mRNA of simian virus 40, the message that codes for the structural coat protein VP1. The length and the nucleotide sequence of the DNA complementary to the 5' end of 16S mRNA indicated that the major leader is 200 nucleotides long and that it is joined to the body of the mRNA 44 nucleotides prior to the initiation codon. A subset of 16S mRNA's with leaders shorter than the main leader may also exist. The method described should be useful for determining spliced junctions both in coding regions in which the sequence of the genome is known but the amino acid sequence of the gene product is not known and in noncoding regions, such as untranslated leader sequences. (42 refs)

- 79-2227 Altered Pattern of Growth and Differentiation in Human Keratinocytes Infected by Simian Virus 40.** (Eng) Steinberg, M. L. (Dept. Pathology, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016); Defendi, V. *Proc Natl Acad Sci USA* 76(2): 801-805; 1979.

Changes in the normal patterns of growth and differentiation resulting from infection of human epidermal cells by simian virus 40 (SV40) were studied. Human epidermal keratinocytes were infected by SV40 in vitro. The structure of the developing keratinocyte colony reflected the spatial separation of cell division and keratinization in intact skin. Thymidine-incorporating cells were primarily localized at the colony periphery whereas nondividing, histologically differentiated cells accumulated in the interior. Viral infection produced a dramatic increase in the size of the proliferative population as, simultaneously, differentiation was reduced in the colony interior. These changes were manifest when SV40 tumor (T)-antigen synthesis was detectable in only a small percentage of the cells; differentiation became increasingly density-dependent as the percentage of T-antigen-positive cells rose over serial passage. The disruption of the normal pattern of growth/differentiation localization coincided with a loss of dependence on serum for growth, but preceded the appearance of other virus-induced properties associated with transformation; ie, the ability to form colonies in soft agar and independence of growth from fibroblasts. (12 refs)

- 79-2228 Enzymatic Activities Associated with a Purified Simian Virus 40 T Antigen-related Protein.**

(Eng) Tjian, R. (Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11524); Robbins, A. *Proc Natl Acad Sci USA* 76(2): 610-614; 1979.

A protein antigenically related to the simian virus 40 (SV40) A gene product was purified to near homogeneity from HeLa cells infected with the adenovirus-SV40 hybrid virus Ad2+D2 and shown to contain ATPase (ATP phosphohydrolase) and protein kinase (ATP: protein phosphotransferase) activity. Both enzymatic activities copurified with the protein through six stages, including 1 gel filtration column, 2 ion-exchange columns, and 1 heparin-affinity column. Analogous fractions from extracts of cells uninfected or infected with Ad2 alone did not contain these enzymatic activities. The D2 hybrid protein resolved into two forms (I and II) during ion-exchange chromatography. Form I, the major species (85%), eluted from diethylaminoethyl (DEAE)-Sephadex in 0.37 M NaCl and was able to catalyze the hydrolysis of ATP to ADP + inorganic phosphate at a rate of 3 micromoles/hr/mg. The remaining 10%-15% of the D2 hybrid protein consisted of form II, which eluted from DEAE-Sephadex in 0.29 M NaCl and was able to hydrolyze ATP as well as to incorporate P from ATP into either the D2 hybrid protein itself or other protein acceptors such as phosphovitin. Although both forms were able to bind DNA, the ATPase activity of form I cosedimented with SV40 DNA more efficiently than did the protein kinase activity of form II during glycerol gradient centrifugation. The ATPase activity of form I was efficiently inhibited by the addition of anti-tumor antigen (anti-T) gamma globulin to the reaction mixture, whereas control gamma globulin had no effect. Similarly, the phosphorylation of the D2 hybrid protein by form II was inhibited by anti-T gamma globulin. By contrast, phosphorylation of phosphovitin was specifically inhibited by antibody only when the immune complex was removed from the reaction mixture. Thus, it appears likely that one and possibly two enzymatic activities are carried out by the D2 hybrid protein. (26 refs)

- 79-2229 Phosphorylation of T-Antigen and Control of T-Antigen Expression in Cells Transformed by**

Wild-Type and *tsA* Mutants of Simian Virus 40. (Eng) Edwards, C. A. (Lab. Molecular Biology, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, Bethesda, MD, 20014); Khoury, G.; Martin, R. G. *J Virol* 29(2): 753-762; 1979.

Chinese hamster lung (CHL) cells transformed by wild-type simian virus 40 (SV40; cell line CHLWT15) or transformed by the SV40 mutants *tsA30* (cell lines CHLA30L1 and CHLA30L2) or *tsA239* (cell line CHLA239L1) were used to determine the rates of turnover and synthesis of the tumor (T)-antigen protein and the rate of turnover of the phosphate group(s) attached to the T antigen at both the permissive and restrictive temperatures. The phosphate group turned over several times within the lifetime of the protein to which it was

attached, with the exception of the phosphate group in the *tsA* transformants at 40 C, which turned over at the same rate as the T-antigen protein. The steady-state levels of the T antigens [mol wts 92,000 (92K) and 17K] and the amount of SV40-specific RNA were also determined in each of the lines. The CHLA30L1 line contained two to three times more early SV40 RNA than the CHLA30L2 line. Although neither line formed colonies in agar at 40 C, CHLA30L1 overgrew a normal monolayer at 40 C. The rate of 92K T-antigen synthesis was 1.5 times faster in CHLA30L1 than in CHLA30L2 at 33 C and 4 times faster at 40 C. The different phenotypes of these two presumably isogenic cell lines seemed to be related to the levels of the T antigens. The ratios of the 92K T antigen to the 17K T-antigen were similar in the two lines. Transformed CHL cell lines, unlike transformed mouse 3T3 cell lines, were found to contain very small amounts of the 56K T antigen. (26 refs)

- 79-2230 Intracellular Forms of Simian Virus 40 Nucleoprotein Complexes. I. Methods of Isolation and Characterization in CV-1 Cells.** (Eng) Fernandez-Munoz, R. (Virologia Centro "Ramon y Cajal", Madrid-34, Spain); Coca-Prados, M.; Hsu, M. T. *J Virol* 29(2): 612-623; 1979.

A new method for isolating intracellular forms of simian virus 40 (SV40) nucleoprotein (NP) complexes from SV40-infected CV-1 cells late in the infectious cycle is described, along with the initial characterization of their physical and biochemical properties. In contrast to the Triton extraction method, which yields only a 60S-70S complex, this new procedure yielded three SV40 NP complexes: complex I, complex II, and the mature virion (V). The three NP complexes differed in physical as well as biochemical properties. Complex I, which is only a small portion of the total SV40 NP complexes late during infection, was active in synthesizing both SV40-specific DNA and RNA. On the basis of its properties, it is suggested that complex I is the active chromatin of SV40. Pulse-labeling experiments suggested the following metabolic pathway: I is converted to II, which in turn is converted to V. Conversion of complex I to II occurred shortly after the completion of SV40 DNA replication and resulted in inactivation of the biosynthetic activities of I. The role of complex II in the SV40 infection cycle is not known. (21 refs)

- 79-2231 Evidence that the RNA Polymerase Usually Does Not Make a Complete Transcript of the Late Strand of Simian Virus 40 DNA.** (Eng) Fried, A. H. (33 Kings Circle, Malvern, PA, 19355). *J Virol* 29(2): 466-474; 1979.

A model for the transcription of the late (L) strand of simian virus 40 DNA, in which late after the infection of permissive monkey cells, RNA polymerase makes a complete transcript of the L DNA strand before terminating transcription, was

evaluated. If the model is correct, the rate of synthesis of all RNA sequences from the L DNA strand should be equal. About one-half of the L DNA strand is transcribed into late messenger RNA (mRNA) sequences and the other half into late degraded RNA (dRNA) sequences, which do not leave the nucleus. Using glucosamine to reduce the size of the intracellular uridine triphosphate pool before and after pulse-labeling CV-1 monkey cells with radioactive uridine, a pulse-chase experiment was performed to determine the half-lives of these sequences. The half-life of the late dRNA sequences was determined to be 4 min. On the av, the late mRNA sequences were degraded more slowly. In a parallel experiment with similarly treated cells, it was shown that after a 2-min label with radioactive uridine, there was only 0.2 times as much radioactivity in the late dRNA sequences as in the late mRNA sequences in the total cellular RNA population. When the results were combined, the rate of synthesis of the late dRNA sequences was calculated to be at most 0.3 times that of the late mRNA sequences. Consequently, the results provide strong evidence that when RNA polymerase transcribes the late mRNA sequences, it usually terminates transcription before all the late dRNA sequences are transcribed. (23 refs)

- 79-2232 Karyology and Tumorigenicity of a Simian Virus 40-Transformed Chinese Hamster Cell Clone.** (Eng) Lehman, J. M. (Dept. Pathology, Univ. Colorado Medical Center, Denver, CO, 80262); Trevor, K. *J Cell Physiol* 98(3): 443-450; 1979.

To determine whether specific chromosomal changes are associated with tumorigenicity, a pseudodiploid clone of Chinese hamster cells transformed in vitro with simian virus 40 (SV40) was injected into nude mice through three successive passages. The cells were cultivated briefly in vitro between each animal inoculation. Palpable nodules of poorly differentiated fibrosarcomas appeared within 10-14 days following injection. The morphology of all tumor cell populations resembled that of the original Wt-2 clone, all in vitro populations cloned from the tumors were 93%-99% SV40 tumor (T)-antigen positive and SV40 V-antigen negative, and all cell populations demonstrated definite modes in the pseudodiploid range. Frequently noted abnormalities included the addition of chromosomes 1 and 2, recurrence of marker chromosomes that were morphologically unidentifiable, loss of one of the two X chromosomes, and loss of autosomes 5, 6, and 11. The X-chromosome deletions occurred with the same frequency in all cell lines, whereas the addition of chromosomes 1 and 2 tended to occur more often in the tumor cell lines than in Wt-2. The appearance of marker chromosomes and the loss of autosomes 5, 6, and 11 were correlated with tumorigenicity. However, there was no association of tumorigenicity with a specific addition or loss of a particular chromosome(s). (17 refs)

79-2233 Expression of SV40-related T-Antigen in Cell Cultures of Human Meningiomas. (Eng) Zang, K. D. (Institut für Humangenetik, Universität des Saarlandes, D-6650 Hamburg/Saar, W. Germany); May, G.; Fischer, H. *Naturwissenschaften* 66(1): 59; 1979.

A positive reaction to at least one of three hamster antisera to simian virus 40 (SV40) T antigen was obtained in 11/27 cell cultures of human meningiomas. When tested by indirect immunofluorescence for the presence of SV40 antibodies, sera from all T-positive meningioma patients reacted positively on SV40-infected CV1 cells. Although 13/23 tested cultures had abnormal karyotypes, no correlation was detected between karyotype and T-antigen reactivity. (7 refs)

79-2234 A Stretch of "Late" SV40 Viral DNA about 400 bp Long Which Includes the Origin of Replication Is Specifically Exposed in SV40 Minichromosomes. (Eng) Varshavsky, A. J. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139); Sundin, O.; Bohn, M. *Cell* 16(2): 453-466; 1979.

DNA fragments produced from formaldehyde-fixed (F-F) or unfixed simian virus 40 (SV40) minichromosomes (mCS's) by multiple-cut restriction endonucleases were examined. Digestion of unfixed mCS's with Hae III generated all 10 major limit-digest DNA fragments as well as partial cleavage products. In contrast, Hae III digestion of the F-F mCS's produced only the F limit-digest fragment, which is located in the immediate vicinity of the origin of replication, spanning nucleotides 5169 and 250 on a previously described DNA sequence map. This 300-base pair (bp) fragment was released as naked DNA from F-F, Hae III-digested mCS's following pronase-sodium dodecyl sulfate (SDS) treatment or SDS treatment alone. In the latter case, the remainder of the mCS retained its compact configuration. Thus, the F fragment in mCS's is not only accessible to Hae III at its ends, but is also neither formaldehyde cross-linked into any SDS-resistant nucleoprotein structure nor topologically "locked" within the compact mCS particle. This same fragment was preferentially produced during the early stages of digestion of unfixed mCS's with Hae III, and its final yield in the exhaustive digest was significantly higher than that of other limit-digest fragments. Similar results were obtained upon digestion of unfixed or F-F mCS's with Alu I. Of approx 20 major limit-digest DNA fragments, only 2 (F and P, encompassing nucleotides 5146 to 190 and 190 to 325, respectively) were produced by Alu I from the F-F mCS's. Mbo I, Mbo II, Hind III, Hin II + III, and Hinf I did not produce any significant amount of limit-digest DNA fragments from F-F mCS's. It is suggested that a specific region of the "late" SV40 DNA approx 400 bp long is uniquely exposed in the compact mCS. This region is the origin of replication, and it contains binding sites for tumor antigen, specific tandem repeated sequences, and, apparently, the promoters for synthesis of late SV40 messenger RNA's. (34 refs)

79-2235 Effect of Alkylation on the Physical Properties of Simian Virus 40 T-Antigen Species. (Eng) Crawford, L. V. (Dept. Molecular Virology, Imperial Cancer Res. Fund, London WC2A 3PX, England); O'Farrell, P. Z. *J Virol* 29(2): 587-596; 1979.

Large and small species of simian virus 40 (SV40) tumor (T) antigen were analyzed by immunoprecipitation and two-dimensional gel electrophoresis, either directly or after reduction and alkylation of the antigens with N-ethylmaleimide. Alkylation improved the resolution of large-T antigen by two-dimensional gel electrophoresis and was necessary for the resolution of small-t antigen. Large T formed a streak from pH 6.5 to 6.9 on isoelectric focusing gels. Small t formed a sharp protein spot at pH 7.2 when subjected to electrophoresis under nonequilibrium conditions. Alkylation decreased the electrophoretic mobility of both T-antigen species. The apparent increase in mol wt may be due to the association of N-ethylmaleimide with the cysteine-rich regions of these proteins. Viable deletion mutants of SV40 that do not induce the synthesis of small t but produce small-t-related polypeptides were used to localize the cysteine-rich region of small-t to between 0.54 and 0.59 units on the genetic map of SV40. (42 refs)

79-2236 Persistence and Recombination of Minicircular SV 40 DNA in Permissive Cells. (Eng) Chowdhury, K. (Institut für Virusforschung, Deutsches Krebsforschungszentrum, Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany); Ruben-Barretto, M.; Sauer, G. *Z Krebsforsch* 93(1): 31-44; 1979.

Deleted microcircular simian virus 40 (SV40) DNA preparations containing 10%-25% deletions were used to transfect permissive CV-1 monkey cells to study whether SV40 DNA can persist in a plasmid-like state. Addition of wild-type DNA to the deleted microcircular DNA prior to transfection permitted the replication of all deleted molecules, but in the absence of complementary helper DNA, only the least-deleted molecules (10%-15% deletion) were able to replicate. When microcircular DNA containing relatively large deletions (15%-25% deletion) was employed for transfection, no viral DNA replication or infectious virus production was detected for up to 4 wk postinfection. Between 5 and 8 wk after infection, however, a cytopathic effect developed, and virus-specific antigens were expressed, replication of SV40 DNA occurred, and viral progeny appeared. The data showed that viral DNA molecules containing deletions that had persisted in the cell for 4 wk in an unexpressed state subsequently recombined to form DNA molecules that gave rise to infectious virions. In no case did a transfected carrier culture contain replicating SV40 DNA in the absence of virion production. (27 refs)

- 79-2237 Nucleotide Sequence at the 5' Terminus of Adenovirus 2 Late Messenger RNA.** (Eng) Lockard, R. E. (Dept. Biology and Center Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139); Berget, S. M.; RajBhandary, U. L.; Sharp, P. A. *J Biol Chem* 254(3): 587-590; 1979.

The nucleotide sequence of the 5'-terminal undecanucleotide common to all the late viral messenger RNA's (mRNA's) synthesized from the region of the adenovirus type 2 (Ad2) genome mapping between 16.0 and 92.0 units was studied. Two-dimensional fingerprint analysis of 5'-³²P-labeled RNA followed by two-dimensional thin-layer chromatography revealed a single oligonucleotide that appeared to be derived from the capped 5' termini of the late Ad2 mRNA's. As determined by a two-dimensional homochromatographic analysis of a partial nuclease P1 digest, the nucleotide sequence of this oligonucleotide was (³²P)m⁶AmCUCUCU-UCCGp. The 5'-terminal undecanucleotide sequence from late Ad2 mRNA was compared with the 5'-terminal nucleotide sequences of human, rabbit, and mouse α - and β -globin mRNA's. Each of these mRNA's contained the sequence ³'CUUPyPyG', which is complementary to the sequence ¹'GAAGGC' present close to the 3' terminus of the 18S ribosomal RNA of most eukaryotes. It should now be possible to locate the major late promoter within the adenoviral genomic DNA sequence. (42 refs)

- 79-2238 Normal Human Tissues Contain RNA and Antigens Related to Infectious Adenovirus Type 2.** (Eng) Jones, K. W. (Inst. Animal Genetics, Univ. Edinburgh, Kings Bldgs., West Mains Road, Edinburgh, UK); Kinross, J.; Maitland, N.; Norval, M. *Nature* 277(5694): 274-279; 1979.

To identify possible human RNA sequences related to adenovirus type 2 (Ad2) viral DNA in uninfected human organs, placenta RNA was hybridized to Ad2 DNA, human DNA, or λ phage DNA. The placenta RNA hybridized to a great degree with the human DNA, to a moderate degree with Ad2 DNA, and not at all with the phage DNA. Hybridization of placenta RNA with restriction endonuclease-digested Ad2 DNA showed four regions of hybridization: the first began (rightward limit) at 7.5 units on the Ad2 map, the second began (leftward limit) at approx 26 units, the third extended from approx 37-58.5 units, and the fourth was between approx 70.7 and 75.9 map units. The first region contains the transforming gene(s) of Ad2. The same pattern was found using RNA from adult human liver and RNA from the liver, kidney, brain, and spleen of a gorilla. RNA's from human cell lines in permanent culture and from chickens showed little or no hybridization. The human placenta RNA-Ad2 DNA hybrids were reasonably thermally stable. Immunologic experiments showed that rabbit cells infected with Ad2 contained certain antigens that were not present in uninfected rabbit or human cells in culture. Some of these antigens were identical to tissue antigens present in most human placenta samples and in gorilla tissues. (32 refs)

- 79-2239 Parental Adenovirus Type 2 Genomes Recovered Early or Late in Infection Possess Terminal Proteins.** (Eng) Straus, S. E. (Dept. Pathology, Washington Univ. Sch. Medicine, St. Louis, MO, 63110); Sergeant, A.; Tigges, M. A.; Raskas, H. J. *J Virol* 29(2): 828-832; 1979.

An attempt was made to determine whether the intranuclear parental DNA of adenovirus 2 is associated with terminal proteins using convenient assay. Restriction fragments bearing terminal proteins aggregate and do not enter agarose gels. Proteolytic digestion of the aggregated complexes liberates equimolar amounts of each terminal fragment, which then migrates normally in the gel matrix. At both early (3 hr) and late (18 hr) times after infection of KB cells with adenovirus 2, > 90% of the parental nuclear viral genomes were found to exist as complexes that contain terminally linked proteins. Density shift experiments employing 5-bromo-2'-deoxyuridine indicated that these parental DNA molecules remain complexed with terminal proteins after DNA replication. The persistent linkage of proteins to the termini of intranuclear viral DNA suggests that these proteins have an essential role in adenovirus replication. (15 refs)

- 79-2240 Regulation of the Appearance of Cytoplasmic RNAs from Region 1 of the Adenovirus 2 Genome.** (Eng) Spector, D. J. (Dept. Pathology, Div. Biology and Biomedical Sciences, Washington Univ. Sch. Medicine, St. Louis, MO, 63110); McGrogan, M.; Raskas, H. J. *J Mol Biol* 126(3): 395-414; 1978.

The time course of appearance of cytoplasmic RNA's coded by the region 0-10.7 on the adenovirus 2 (Ad2) genome (early region 1) was examined using specific DNA probes. Hybridization with restriction endonuclease fragments of viral DNA resolved five cytoplasmic RNA's (22S, two 13S, two 9S RNA's). The 22S RNA contained sequences to the right of map position 4.4. 13S-L RNA mapped to the left of position 4.4, and 13S-f RNA was transcribed from two separate regions to the right of 4.4. Each 13S RNA shared 3' sequences with a distinct 9S RNA. 9S-L RNA mapped to the left of 4.4, and 9S-polypeptide IX (9S-IX) hybridized only to the 8.7-10.7 fragment [8.7-10.7 RNA is the messenger RNA (mRNA) for polypeptide IX]. Sequences in 13S-f RNA were also present in the 22S species. During productive infection, each RNA species had a characteristic rate of appearance in the cytoplasm. 22S and 13S-L RNA accumulated at a constant rate throughout infection. Initially, 13S-f RNA appeared at a substantially lower rate than 22S and 13S-L RNA's. At late times, accumulation of 13S-f RNA was stimulated > 50-fold, until its appearance exceeded that of the other early RNA's. The 9S RNA's were detected only after viral DNA replication had begun. The rate of appearance of each approached that of its colinear 13S RNA. The results show that there is a complex regulatory pattern for region 1 RNA's. (48 refs)

- 79-2241 Adenovirus Aggregation and Preservation in Extracellular Environment.** (Eng) Galdiero, F. (Cattedra Facolta di Medicina e Chirurgia 1, Universita di Napoli, Istituto di Microbiologia, S. Andrea della Dame 2, 80138 Naples, Italy). *Arch Virol* 59(1/2): 99-105; 1979.

Sucrose gradient velocity sedimentation studies demonstrated that adenovirus type 2 aggregation depends on: ionic strength, which must be between 0.005 and 0.05 M NaCl; pH, with 90% aggregation occurring at pH 4-5; particle concentration, which was optimum at 5×10^{11} particles/ml; and temperature (25-37 C). Below 20 C, aggregation decreases, and below 4 C no aggregation occurs. (15 refs)

- 79-2242 Structure of the Components of the Adenovirus-Simian Virus 40 Hybrid Population Ad2++HEY And Reciprocal Molecular Interactions.** (Eng) Van Roy, F. (Lab. Molecular Biology, State Univ. Ghent, Ledeganckstraat 35, 9000 Ghent, Belgium); Fiers, W. *J Mol Biol* 126(4): 691-720; 1978.

The different components of the adenovirus type 2 (Ad2)-simian virus 40 (SV40) hybrid population Ad2++HEY were purified, and their structures and reciprocal interactions in African green monkey kidney cells were studied. Two of the three defective hybrid virions in Ad2++HEY, HEY-1.4 and HEY-2.4, contained more than one complete SV40 genome length, with the excess SV40 DNA being arranged in head-to-tail tandem repetition. In the presence of helper Ad2 virions, the HEY-1.4 and HEY-2.4 particles interconverted readily in the monkey cells, and they were present in their original relative amounts (HEY-1.4 particles were most numerous). With helper Ad5 virions, however, HEY-2.4 particles predominated. Although HEY-1.4 particles were normally more abundant in the population, they showed less ability to yield nonhybrid SV40 progeny than the HEY-2.4 particles. Excision of SV40 DNA from the HEY-1.4 genome was found to be an accurate process, and there was no evidence of the acquisition of Ad-specific or host cellular DNA sequences. Although the genome of the excised nonhybrid SV40 progeny differed slightly from that of SV40 strain 776, there was no reason to believe that these changes were causally related to the integration and excision phenomena. (62 refs)

- 79-2243 Simian Virus 40 Specific Proteins on Surface of HeLa Cells Infected with Adenovirus 2-SV40 Hybrid Virus Ad2+ND2.** (Eng) Deppert, W. (Max Planck Inst. Biophysical Chemistry, PO Box 968, D-3400 Gottingen, W. Germany); Pates, R. *Nature* 277(5694): 322-324; 1979.

Immunofluorescence microscopy using a rabbit anti-T serum prepared against purified denatured tumor (T)-antigen was used to visualize simian virus 40 (SV40)-specific proteins on the cell surface of HeLa cells infected with the nondefective

adenovirus 2-SV40 hybrid virus Ad2+ND2. The rabbit anti-T serum specifically precipitated the SV40-specific 56,000-dalton (56K) and 42K proteins. Staining with this serum revealed perinuclear or cytoplasmic U-antigen fluorescence in about 80% of the Ad2+ND2-infected cells. Ad2-infected HeLa cells treated with the rabbit anti-T serum did not exhibit any fluorescence staining. The nuclei of cells fixed with methanol-acetone, but not those of cells fixed with formalin, were stained by the serum. Formalin-fixed Ad2+ND2-infected HeLa cells stained with rabbit anti-T serum showed cell-surface fluorescence, indicating that the surface fluorescence was associated with the Ad2+ND2-infected cells. No cell-surface fluorescence was obtained when Ad2+ND2-infected cells were stained after extensive absorption of the serum on methanol-fixed SV101 cells, a procedure that reduced T- and U-antibody titers by 80%. The data provide evidence that at least part of the SV40-specific 56K and 42K proteins located in the plasma membranes of Ad2+ND2-infected cells are located on the cell surface. This location is compatible with the hypothesis that these proteins carry the antigenic determinants for SV40 tumor-specific transplantation antigen. (18 refs)

- 79-2244 Simian Virus 40 T- and U-Antigens: Immunological Characterization and Localization in Different Nuclear Subfractions of Simian Virus 40-transformed Cells.** (Eng) Deppert, W. (Max Planck Inst. Biophysical Chemistry, D-3400 Goettingen, W. Germany). *J Virol* 29(2): 576-586; 1979.

Simian virus 40 (SV40)-transformed 3T3 cells (clone SV101) and HeLa cells infected by the nondefective adenovirus 2 (Ad2)-SV40 hybrid viruses Ad2+ND1 and Ad2+ND2 were analyzed for SV40 tumor (T) and U antigens, respectively, using Syrian golden hamster SV40 tumor sera before and after they were absorbed to remove U antibodies. The results showed that T- and U antigens could be defined by separate classes of antigenic determinants and that the U antigen determinants in SV40-transformed cells and in hybrid virus-infected cells were similar. The apparent discrepancy in the subcellular location of U antigen in SV40-transformed cells (nuclear location) and in hybrid virus-infected cells (perinuclear location), as determined by immunofluorescence staining of methanol/acetone-fixed cells, could be resolved by treating hybrid virus-infected cells with a hypotonic KCl soln before fixation. After this treatment, hybrid virus-infected cells also showed nuclear U antigen staining. The possibility of an association of T and U antigens with different nuclear subfractions in SV40-transformed cells was investigated. SV40-transformed cells were lysed with hypotonic buffer containing Nonidet P-40, and the nuclei were further divided into a nuclear matrix fraction and a high-salt nuclear extract. Analysis of the nuclear matrices by immunofluorescence microscopy with T+U+ and T+U- hamster SV40 tumor serum revealed that U antigen remained associated with the nuclear matrices, whereas T antigen could not be detected in this nuclear subfraction. However, T antigen could be im-

munoprecipitated from the nuclear extracts of the SV40-transformed cells. (38 refs)

- 79-2245 Transformation of Rat Cells by the Hybrid Virus Ad2⁺ HEY.** (Eng) Galloway, D. A. (Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11524); Lukanidin, E.; Topp, W. C.; Sambrook, J. *J Gen Virol* 42(2): 339-356; 1979.

Four Fischer rat embryo cell lines transformed with DNA from a hybrid simian virus 40 (SV40)-adenovirus 2 (Ad2) virus, adenovirus 2 HEY (Ad2⁺ HEY), were studied with respect to phenotypic characteristics, synthesis of virus antigens, rescue of SV40 genomes, content of virus DNA, and the arrangement of integrated virus DNA sequences. All four transformed cell lines synthesized SV40 tumor (T) antigen, but only one expressed Ad2 T antigen. None of the transformed cell lines expressed late antigens; eg, SV40 V antigen or Ad2 fiber antigen. This pattern of virus antigen expression suggests that the cell lines were transformed by the SV40 moiety of the hybrid virus. SV40 could be rescued from 3/4 cell lines by fusion with permissive cells. No Ad2 DNA sequences were detected in the rescued genomes. Three cell lines contained 0.5-2 copies of SV40 and Ad2 DNA sequences per diploid quantity of rat cell DNA. The fourth line contained 5 copies of SV40 DNA and 20 copies of the Ad2 genome. At least three of the cell lines contained DNA sequences from the helper Ad2 in addition to sequences from the Ad2⁺ HEY genome. The location of the virus DNA sequences among the products of digestion of transformed rat cell DNA by restriction endonucleases was determined by hybridization. The pattern that emerged was very complex, suggesting multiple insertions of both adenovirus and SV40 DNA sequences. The findings indicate that Ad2⁺ HEY sequences are integrated into the DNA of the transformed cell lines and cause these cells to express virus antigens and have the phenotype of transformed cells. (43 refs)

- 79-2246 Immunoprecipitation of Protein Kinase Activity from Adenovirus 5-infected Cells Using Antiserum Directed Against Tumour Antigens.** (Eng) Lassam, N. J. (Dept. Biology, McMaster Univ., Hamilton, Ontario, Canada L8S 4K1); Bayley, S. T.; Graham, F. L.; Branton, P. E. *Nature* 277(5693): 241-243; 1979.

Studies were conducted to determine if the transforming gene products of human adenovirus type 5 (Ad5) possess protein kinase activity. Antiserum against viral transformation proteins was obtained from hamsters bearing tumors induced by Ad5-transformed hamster cells. Cytoplasmic extracts were prepared from Ad5-infected and mock-infected human KB cells and immunoprecipitated with immune or control nonimmune serum. Washed immune complexes were then incubated in the presence of [γ -³²P]ATP, and the samples were analyzed by sodium dodecyl sulfate-polyacrylamide gel

electrophoresis. The results indicate that an Ad5 transformation-specific protein is either a protein kinase or is associated with one. Whether this activity is due to a virus-coded or virus-induced cellular enzyme is not clear. With transformation-defective host range mutants of Ad5, enzyme activity was reduced, suggesting that these mutants are at least partly deficient in this function. These results are similar to those obtained with Rous sarcoma virus and indicate that protein kinase activity is associated with the transforming proteins of both an RNA and a DNA tumor virus. Therefore, alterations in protein phosphorylation may be a general mechanism by which all tumor viruses induce cellular transformation. (14 refs)

- 79-2247 Autoregulation of Adenovirus Type 5 Early Gene Expression. III. Transcription Studies in Isolated Nuclei.** (Eng) Blanton, R. A. (Dept. Microbiology, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033); Carter, T. H. *J Virol* 29(2): 458-465; 1979.

To analyze the mechanism behind the overproduction of early virus RNA by an early temperature-sensitive mutant (*ts* 125) of adenovirus type 5 (Ad5) at the restrictive temperature, the rate of adenovirus RNA synthesis was compared in nuclei isolated from cells infected with Ad5 or *ts*125. The cells were infected at 40.5 C in the presence of the DNA synthesis inhibitor 1- β -D-arabinofuranosylcytosine. In nuclei isolated at various times postinfection (PI), the maximum amount of virus RNA synthesis occurred at 6 hr PI, after which time virus RNA synthesis declined in nuclei from wild-type infections but remained high in nuclei from *ts*125 infections. At 12 hr PI, the amount of virus RNA synthesis was 8- to 11-fold higher in nuclei from *ts*125 infections than in nuclei from wild-type infections. However, the kinetics of virus RNA synthesis in nuclei isolated from both infections were similar. When a *ts*125-infected culture was shifted to 32 C for 3 hr (12-15 hr PI) before nucleus isolation, the amount of virus RNA synthesis in the isolated nuclei was reduced to nearly wild-type levels. A pulse-chase experiment showed little difference in degradation rates of virus RNA in isolated nuclei from wild-type and *ts*125 infections. Hybridization of RNA synthesized in vitro to restriction fragments of Ad5 DNA was consistent with early virus RNA. These results support the idea that the 72,000-dalton DNA-binding protein encoded by the mutant gene in *ts*125 can regulate early adenovirus gene expression by inhibiting initiation of transcription of the adenovirus genome. (30 refs)

- 79-2248 Virus-associated RNA Synthesis in Adenovirus Type 12 Infections (Meeting Abstract).** (Eng) Geis, A. (Dept. Pathology, CMDNJ-Rutgers Medical Sch., Piscataway, NJ, 08854); Fohring, B.; Raska, K. *Fed Proc* 38(3, part 2): 1071; 1979. (no refs)

79-2249 Activation of an Endogenous Oncogenic Virus by Human Adenovirus in Mice. (Eng) Ohmori, M. (Dept. Pathology, Okayama Univ. Medical Sch., Okayama 700, Japan); Ohtsuki, Y.; Kobayashi, S. *Z Krebsforsch* 93(1): 45-56; 1979.

The oncogenicity of viral particles prepared from adenovirus type 12 (Ad12)-induced tumors in C3H/BiF mice was studied. The intracisternal and intercellular virus particles found in the Ad12-induced tumors resembled A- and C-type particles. Within 24 mo after they were inoculated with a cell-free extract from these tumors, 12/40 mice developed malignant lymphomas. Analysis of four of these lymphomas revealed lymphocytic leukemia in three cases and myeloid leukemia in one. The induced lymphomas contained occasional virus particles resembling intracisternal A particles and immature C-type particles. Only a few intracisternal A particles and C-type particles were found in two spontaneous hepatomas and in 4-nitroquinoline 1-oxide-induced tumors in C3H/BiF mice. Furthermore, only the original Ad12-induced tumor cells were shown to contain tumor-specific antigen by fluorescence microscopy. The fluorescent antigens were associated with the intracisternal A particles but not the C-type particles. The induced lymphomas and the spontaneous hepatomas did not contain tumor-specific antigen. The endogenous intracisternal A- and/or C-type virogenes might be activated by Ad12, causing their appearance in the tumor cells. These viruses may be responsible for the induction of malignant lymphoma. (37 refs)

79-2250 A Model for Assembly of Type-C Oncornaviruses. (Eng) Bolognesi, D. P. (Dept. Surgery, Duke Univ. Medical Center, Durham, NC, 27710); Montelaro, R. C.; Sullivan, S. J.; Frank, H.; Schafer, W. *Med Microbiol Immunol (Berl)* 164(1/3): 97-113; 1977.

The morphology and structural components of C-type oncornaviruses are discussed in relation to a proposed model for the assembly of these viruses. According to this model: (a) complexes of virus envelope components migrate to the cell surface and are inserted in the membrane at the site of virus budding; (2) uncleaved precursor molecules to the internal virus polypeptides are transported to the budding site; (3) proteolytic enzymes cleave the precursor molecules at the appropriate sites, generating individual structural elements of the virus; and (4) the virion components associate with themselves and/or other molecules to form the substructures found in the mature virus. (62 refs)

79-2251 Role of RNA Polymerase II in Type C Virus Induction (Meeting Abstract). (Eng) Snead, R. M. (Frederick Cancer Res. Center, Frederick, MD, 21501); Ramsburg, M. E.; Long, C. W. *Fed Proc* 38(3, part 1): 812; 1979. (no refs)

79-2252 Type C Virus Induced by Iododeoxyuridine in the Human Embryonic Cell Strain HEL-12. (Eng) Prochownik, E. V. (Dept. Pathology, Div. Biological Sciences, Univ. Chicago, Chicago, IL, 60637); Panem, S.; Kirsten, W. H. *J Gen Virol* 42(2): 399-403; 1979.

The induction of a C-type virus from a strain of human embryonic lung cells (HEL-12) by iododeoxyuridine (IUdR) was examined at various times during in vitro propagation. IUdR did not elicit C-type virus production immediately following initiation of cultures from frozen primary HEL-12 cells. After overnight treatment with 30 µg/ml IUdR, the cells expressed viral antigens and produced a C-type virus between the 25th and 80th day of in vitro growth. Production of the induced C-type virus was transient. Single-cell clones of the parental HEL-12 strain were likewise susceptible to C-type virus production by IUdR. During the interval of spontaneous C-type virus production and max antigen expression, which occurred between 80 and 120 days of in vitro growth, virus yield was not enhanced by the addition of an otherwise virogenic dose of IUdR to the growth medium of uncloned HEL-12 cells. (13 refs)

79-2253 In-Vivo Expression of a C-Type RNA Virus in Rat Ventral Prostate Epithelial Cells. (Eng) Anderson, K. M. (Oncology Lab., Dept. Medicine, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL, 60612); Rubenstein, M.; Seed, T. M. *Biochem Biophys Res Commun* 86(2): 402-406; 1979.

During evaluation of a procedure for separating rat ventral prostate epithelial cells from connective tissue cells, isolated fractions were examined by transmission electron microscopy. Characteristic C-type RNA viruses were seen budding from or in close proximity to the plasma membranes of isolated epithelial cells. Most of the particles were associated with fraction 4 at the gradient cushion interface, which is enriched in epithelial cells. Similar particles were much less evident in fractions containing fewer epithelial cells (fractions 1-3) and in intact prostatic tissue. The particles were not associated with cells of connective or vascular tissue origin. To date, 3/5 individually processed rat prostates were positive for the virus: 2/3 glands were from Sprague-Dawley rats, and one was from a Long-Evans rat. The prostate from a Wistar rat appeared negative. Dissociation of the prostatic tissue and sedimentation of the cells through a Ficoll gradient facilitated detection of the virus. (14 refs)

79-2254 Characterization of a Retrovirus Isolated from Normal Mink Cells Co-cultivated with a Dog Mammary Tumour. (Eng) Ahmed, M. (John Smith Memorial Cancer Res., Pfizer Inc., Maywood, NJ, 07607); Yeh, J.; Stephens, R.; Holden, H. E.; Schlom, J.; Drohan, W.; Howard, D. K. *J Gen Virol* 42(1): 179-184; 1979.

A retrovirus antigenically distinct from known B-, C-, and D-type viruses was isolated from normal mink (*Mustela vison*) lung cells that had been cocultivated with 5-iododeoxyuridine- and dexamethasone-treated dog mammary tumor cells. Cytogenetic studies of the virus-releasing coculture showed mitotic figures identical to the normal mink cell line (Mv1Lu) except for a low frequency of cells with extensive chromosomal breakage and uncoiling. The new virus had a buoyant density of 1.16 g/ml and contained 60S RNA and a reverse transcriptase that preferred Mn^{2+} over Mg^{2+} for DNA synthesis. This enzyme utilized poly(rA).oligo(dT) more efficiently than poly(dA).oligo(dT), and it could synthesize DNA copies from endogenous RNA. Morphologically, it was a typical C-type virus. The virus readily infected mink, dog, and other mammalian cells. Hybridization studies showed that normal mink DNA contains multiple copies of proviral sequences of this newly isolated virus. Serological analyses indicated that the mink endogenous virus contains in its core protein, in addition to the interspecies C-type determinant, an antigenic component related to one of the determinants found in feline leukemia virus p30 protein. This determinant is not present in the Rauscher leukemia virus, RD114 virus, or simian sarcoma virus. Mink cells maintained for > 2 yr showed no spontaneous release of a retrovirus. This suggests that coculturing of mink cells with other cell lines may provide the necessary information for active multiplication of endogenous C-type virus in mink cells. (14 refs)

- 79-2255 Studies of an RNA Virus Isolated from a Human Histiocytic Lymphoma Cell Line.** (Eng) Kaplan, H. S. (Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305). *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 695-706; 1978.

The characteristics and infectivity of a C-type RNA virus isolated from a permanent cell line (SU-DHL-1) established from a patient with diffuse histiocytic lymphoma (DHL) were studied. The SU-DHL-1 virus has many of the characteristics of other mammalian C-type RNA viruses: endogenous reverse transcriptase (RT) activity inhibitable by antibodies to subhuman primate viral RT's, the capacity to induce syncytia in rat XC cells, and typical electron microscope morphology. The supernatant culture fluids of 4/7 other histiocytic lymphoma cell lines assayed contained significantly elevated levels of RT-like activity. One of these cell lines, SU-DHL-2, also induced typical syncytia when cocultivated with rat XC cells. The virus was noninfectious for a spectrum of human and other mammalian normal and neoplastic cells of nonhematopoietic origin, but it readily infected another human malignant lymphoma cell line, SY-AmB-3, established from a patient with North American Burkitt's lymphoma. After infection, SY-AmB-3 cells revealed the presence of cytoplasmic viral antigens by indirect immunofluorescence, released sustained high levels of RT-like activity into the supernatant culture fluids, and acquired the capacity to induce syncytia when cocultivated with rat XC cells. Human

and rhesus monocytes and possibly human B, but not T, lymphocytes exhibited unusual changes in their growth behavior in vitro following infection with the SU-DHL-1 virus, as well as morphologic and cytogenetic abnormalities. The biological significance of these changes is not yet known. (34 refs)

- 79-2256 Human Hematopoietic Cells: A Search for Retrovirus-related Information in Primary Tissues and Development of Liquid Suspension Culture Systems for Studies of Cell Growth and Differentiation and of Virus-Cell Interactions.** (Eng) Gallo, R. C. (Lab. Tumor Cell Biology, NCI, Bethesda, MD, 20014); Gallagher, R. E.; Ruscetti, F. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 671-694; 1978.

Studies examining primary human hematopoietic tissues for the presence of retrovirus information and the development of liquid suspension culture systems for human hematopoietic cells are reviewed. Available data indicate that humans have endogenous viral genes. Several investigations are consistent with the idea that tissues from some leukemia-lymphoma patients contain acquired viral information: antibodies in sera from leukemic patients reacted with the reverse transcriptase from some of the C-type primate viruses, and molecular hybridization has revealed sequences in the DNA from a few leukemic patients that were homologous with sequences in murine or primate C-type viruses. C-type virus production has been observed in only 1/38 lines of myelogenous leukemia cells that actively replicated in liquid suspension culture for 6 wk. Human T lymphocytes and myeloid cells were grown in liquid suspension culture, and a human myeloid cell line was established in which the cells maintained a stable promyelocyte morphology. Most types of blastic WBC cultures were readily infected by primate C-type viruses, but continuously replicating, differentiated T-cell strains, short-term cultures of differentiated myeloid cells, and two blastic Epstein-Barr virus (EBV)-negative lines were not susceptible to productive infection. Other studies of the infection of human WBC with C-type viruses suggest that the effect of the C-type viral infectivity procedures may be mediated if the transforming effect of EBV is promoted. (56 refs)

- 79-2257 Genome RNA Dependence of Reovirus-associated Enzyme Activities Measured by Photo-reaction with Psoralen Derivatives (Meeting Abstract).** (Eng) Nakashima, K. (Roche Inst. Molecular Biology, Nutley, NJ, 07110); Shatkin, A. J. *Fed Proc* 38(3, part 1): 814; 1979. (1 ref)

- 79-2258 Purification of a Soluble and Template Dependent Poliovirus RNA Polymerase that Copies Vi-rion RNA In Vitro (Meeting Abstract).** (Eng) Van Dyke, T. A. (Univ. Florida, Gainesville, FL, 32610); Flanagan, J. B. *Fed Proc* 38(3, part 1): 226; 1979. (no refs)

- 79-2259 Fanleaf of Vine Plants and the Etiology of Cancer.** (Fre) Bosc, M. (Laboratoire d'Histologie, Institut Bouisson-Bertrand, 5 rue Ecole-de-Medecine, 34000 Montpellier, France). *Trav Soc Pharm Montp* 38(3): 221-235; 1978.

The biochemical characteristics of fanleaf, a viral disease of vine plants, and cancer are compared. The vegetative organs of vine plants affected by fanleaf are characterized by intense glycogenesis and the absence of polyphenols, whereas anaerobic glycolysis and the presence of polyphenols are typical traits of tumor tissues. The anaerobic glycolysis in tumor tissues is linked with the appearance of pyruvate kinase isoenzymes. Unlike the situation in tumor tissues, tryptophan metabolism is inhibited in the diseased vine plants. The enzymatic differences between cancer and fanleaf suggest that the latter may be useful as a model for studying enzymatic mechanisms capable of repressing tumor growth. (15 refs)

- 79-2260 In Vitro Transformation of Cultured Cells from *Nicotiana tabacum* by *Agrobacterium tumefaciens*.** (Eng) Marton, L. (Inst. Plant Physiology, Biological Res. Center, P.O. Box 521, H-6701 Szeged, Hungary); Wullems, G. J.; Molendijk, L.; Schilperoort, R. A. *Nature* 277(5692): 129-131; 1979.

The in vitro transformation of cells from *Nicotiana tabacum* by various strains of *Agrobacterium tumefaciens* was studied. The tobacco cells were mixed with one of the virulent bacterial strains (LBA 4013, LBA 4001, and LBA 305) or one of the nonvirulent strains (LBA 4011 and LBA 301) for 32 hr. The cells were then cultured in medium supplemented with hormones, followed by subculture in medium without hormones. Colonies, which were scored after a 7-wk culture period, were observed only when the tobacco cells were incubated with one of the virulent strains of *A. tumefaciens*. Most of the transformed calli retained the ability to proliferate hormone independently after subsequent passages on hormone-free medium. Some of these calli also demonstrated lysopine dehydrogenase (LpDH) activity. Calli obtained in vivo after wounding and infection of plants with the same virulent bacterial strains always contained both tumor markers, and they retained both markers after cloning and subculturing for > 2 yr. LBA 4013 had the highest transformation

efficiency of the three virulent strains, which might be related to its ability to transmit the tumor-inducing (TI) plasmid to other bacteria in a high frequency. Preliminary results from experiments using purified TI-plasmid DNA as the transforming vehicle indicate that TI DNA alone is sufficient for tumor induction in cultured plant cells. (17 refs)

- 79-2261 Involvement of DNA Gyrase in Replication and Transcription of Bacteriophage T7 DNA.** (Eng) De Wyngaert, M. A. (Dept. Biology, Univ. Rochester, Rochester, NY, 14627); Hinkle, D. C. *J Virol* 29(2): 529-535; 1979.

The effect of coumermycin (CM), an inhibitor of *Escherichia coli* DNA gyrase, on the kinetics of DNA, RNA, and protein synthesis during bacteriophage T7 infection of *E. coli* was investigated using strains resistant (NI 748) and sensitive (NI 747) to CM. Growth of T7 in the CM-sensitive strain was reduced to 20% of the control values at 10 µg/ml CM, whereas growth in the resistant strain was unaffected. The rate of DNA and RNA synthesis was significantly reduced in the presence of CM in NI 747 but not in NI 748. Protein synthesis was also inhibited in the CM-sensitive strain, but not as much as DNA and RNA synthesis. Synthesis of T7 early proteins, the products of genes that are transcribed by *E. coli* RNA polymerase and are expressed immediately after infection, was not affected by CM. Synthesis of many of the late proteins, however, was severely inhibited by CM. It is concluded that *E. coli* DNA gyrase may play an important role in the transcription as well as in the replication of T7 DNA. (26 refs)

See also:

- *(Rev.): 79-1818, 79-1835, 79-1836, 79-1837, 79-1838, 79-1839, 79-1840, 79-1841, 79-1842, 79-1843, 79-1844, 79-1845.
*(Chem.): 79-2032, 79-2062.
*(Immun.): 79-2271, 79-2277, 79-2281, 79-2289.
*(Path.): 79-2294, 79-2295, 79-2302, 79-2344.
*(Epid.-Biom.): 79-2345.

- 79-2262 Correlating Terminal Deoxynucleotidyl Transferase and Cell-Surface Markers in the Pathway of Lymphocyte Ontogeny.** (Eng) Silverstone, A. E. (Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Rosenberg, N.; Baltimore, D.; Sato, V. L.; Scheid, M. P.; Boyse, E. A. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book A), 528 pp.; 433-453; 1978.

Evidence is presented that terminal deoxynucleotidyl transferase (TdT) is found in cells developmentally intermediate between the colony-forming units-spleen (CFU-S) and the mature T and B effector cells. The presence of TdT in developing thymocytes but not in circulating T cells is mirrored by its presence or absence in tumor populations of corresponding phenotypes. The more differentiated a T cell becomes, the less TdT it has, and the more differentiated the tumor cell line is with respect to its surface antigens, the less TdT is evident. The tumor cells studied generally had the properties of differentiating cells, such as the Sc-1 antigen, a surface antigen on pluripotent stem cells, TdT, and the thymus-leukemia (TL) antigen. Analysis of human tumors indicated that the major class of acute lymphoblastic leukemia (ALL) has cells with high TdT and a potential relationship to B cells. The occurrence of these human cells encourages a belief that there may be a stage of pre-B cells with a high level of TdT. Normal murine bone marrow contained a small percentage of cells that had very high levels of TdT. About 50% of bone marrow TdT occurred in cells carrying the Lyb-2 alloantigen, a B-cell marker. TdT in normal bone marrow was associated with cell sets carrying Lyb-2 and Sc-1. More than 85% of the total TdT in bone marrow was demonstrated to reside in the 40% or less of cells classified as either prothymocytes (Thy-1 inducible) or Lyb-2 positive. These results indicate that TdT, both in normal cells and tumor cells, appears only in developing cells of the lymphocyte pathway and not in functional cells or tumor homologs of functional cells. (61 refs)

- 79-2263 An Immunoregulatory Factor Associated with Spleen Cells from Tumor-bearing Animals. III. Characterization of the Factor's Target Cells.** (Eng) Isakov, N. (Dept. Cell Biology, The Weizmann Inst. Science, Rehovoth 76100, Israel); Hollander, N.; Segal, S.; Feldman, M. *Int J Cancer* 23(3): 410-414; 1979.

The target cell for the activity of an immunoregulatory enhancing factor (EF) associated with spleen cells from tumor-bearing mice was investigated. EF has been found to potentiate the generation of antibody-producing cells. In the present experiment, EF potentiated antibody production only

in adult thymectomized, nude, and B (adult thymectomized mice lethally irradiated and reconstituted with syngeneic fetal liver cells) mice; i.e., those devoid of mature T lymphocytes. Mice were then immunized with sheep RBC (SRBC) as carrier or with chicken RBC coupled to 4-hydroxy-3-iodo-5-nitrophenylacetylazide (NIP-chicken RBC) as a source of NIP-specific primed B cells in the presence or absence of EF. Various combinations of spleen cells from the donor immunized mice were transferred with NIP-SRBC to lethally irradiated recipient mice. EF did not potentiate helper function except when primed B cells were used, whereas a clear activation or clone expansion of hapten-specific B cells was observed. In contrast, a clear activation or clone expansion of hapten-specific B cells was observed. The data indicate that the EF from tumor-bearing animals directly affected the antigenic triggering of B lymphocytes and their subsequent proliferation and differentiation to antibody-producing cells. (15 refs)

- 79-2264 Role of Different T Cell Sets in the Rejection of Syngeneic Chemically Induced Tumors.** (Eng) Shimizu, K. (1st Dept. Internal Medicine, Nagoya Univ. Sch. Medicine, Nagoya, Japan); Shen, F. W. *J Immunol* 122(3): 1162-1165; 1979.

To ascertain the participation of T lymphocytes in the rejection of syngeneic chemically induced tumors, viable dissociated cells of a methylcholanthrene-induced C57BL/6 (B6) sarcoma were combined with peritoneal cells from highly immunized syngeneic B6 donors and inoculated sc into untreated syngeneic B6 mice. Nonadherent immune peritoneal cells (NA.IPC) protected the B6 recipients from progressive tumor growth under these conditions. The protection was against the specific sarcoma against which the donor mice had been immunized and was achieved with NA.IPC:tumor cell ratios of less than 1:4. The protective NA.IPC cells were T cells, as shown by the fact that elimination of the Thy-1(+), Lyt-1(+), Lyt-2(+), or Lyt-3(+) population abolished protection. Treatment of NA.IPC with α -Lyt-1.2 serum abolished protection as a specific result of the elimination of Lyt-1(+) cells. Antigenic specificity for the Lyt-2 and Lyt-3 systems was also shown. Protection by NA.IPC cells could not be restored by combining Lyt-1 and Lyt-23 cell sets selected from the NA.IPC populations. The data are consistent with the hypothesis that cell-mediated cytotoxicity is an exclusive function of Lyt-23:CS (cytotoxicity; suppression) cells and that these, and possibly Lyt-1:H (helper) amplifier cells, are generated during the assay from a specifically primed antecedent Lyt-123:ARC (antigen-reactive celi) cell set. (14 refs)

79-2265 Differentiation of Precursor Cytotoxic T Lymphocytes Following Alloantigenic Stimulation.

(Eng) Sundharadas, G. (Immunobiology Res. Center, Univ. Wisconsin, Madison, WI, 53706); Sopori, M. L.; Hayes, C. E.; Narayanan, P. R.; Alter, B. J.; Bach, M. L.; Bach, F. H. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book A), 528 pp.; 519-528; 1978.

Factors required for an optimal cytotoxic response following alloantigenic stimulation were investigated in the mixed-leukocyte culture (MLC) and cell-mediated lympholysis assays. In studies of the effect of MLC supernatant on the generation of cytotoxic T-lymphocytes (Tc), the supernatant of an allogeneic MLC resulted in a very significant expansion of the level of the cytotoxic response whereas the supernatant from a syngeneic MLC had no effect. Results of experiments in which an agar system was used indicate that the precursor Tc must have received other signals, in addition to the cytotoxic-defined (CD) antigen stimulus, for the initiation and expansion of the development of Tc to have occurred. The results also suggested that a normal MLC under the agar layer was capable of producing soluble factors that could diffuse through the agar and provide the additional second signal needed for the development of Tc from precursor Tc. The effects of poly A:U and lipopolysaccharide (LPS) on the development of Tc indicate that LPS and poly A:U may enhance cytotoxic responses by different mechanisms. Poly A:U may only be able to amplify an ongoing cytotoxic response, but LPS may have the capacity to promote the initiation of a cytotoxic response as well as to amplify it. Under the conditions used, poly A:U required the presence of adherent cells for its action, whereas LPS did not, which also suggests that the two agents exert their effect at two different steps in the development of Tc. (12 refs)

79-2266 Murine IgD and B-Lymphocyte Differentiation.

(Eng) Uhr, J. W. (Dept. Microbiology, Univ. Texas Southwestern Medical Sch., Dallas, TX, 75235); Cambier, J. C.; Ligler, F. S.; Kettman, J.; Vitetta, E. S.; Zan-Bar, I.; Strober, S. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book A), 528 pp.; 505-518; 1978.

Subsets of B cells were separated on the basis of cell-surface isotype, and their immune function was characterized along with the role of IgM and IgD in the induction of immunologic tolerance and in triggering were determined. Membrane IgD clearly develops late in antigen-dependent B-cell differentiation. The following sequence is proposed: cells bearing only IgM ($\mu+$) acquire IgD, thereby expressing two isotypes ($\mu+\delta+$), and then some of the $\mu+\delta+$ cells lose surface IgM to become cells that bear only IgD ($\delta+$). The IgM receptor alone plays a critical role in the response to thymus-independent (TI) antigens, but both the IgM and IgD receptors are involved in the response to thymus-dependent (TD) antigens. $\gamma+$ cells are also present, and they are involved in producing only IgG responses to TD antigens. Membrane IgD appears to play an important role in the sig-

nal discrimination between tolerance induction and triggering of $\mu+\delta+$ cells. The acquisition of IgD confers resistance to induction of tolerance upon TD antigen-reactive cells but not TI antigen-reactive cells. Since both isotypes are needed to trigger a $\mu+\delta+$ cell, three signals may be needed for stimulation, since T help is also essential. (22 refs)

79-2267 Malignant Transformation of Tracheobronchial Juvenile Papillomatosis Without Prior

Radiotherapy. (Eng) Siegel, S. E. (Div. Hematology-Oncology, Childrens Hosp. Los Angeles, 4650 Sunset Blvd., Los Angeles, CA, 90027); Isaacs, H.; Cohen, S. R.; Stanley, P. *Ann Otol Rhinol Laryngol* 88(2,part 1): 192-197; 1979.

A case of fatal squamous cell carcinoma of the trachea and bronchi developed in a 19-yr-old man who had been previously tracheotomized to relieve obstruction from recurrent laryngeal papillomas. The patient had undergone prolonged tracheotomy and numerous laryngoscopic and bronchoscopic procedures since the age of 4 yr for recurrent laryngeal papillomas. Recurrent tracheal papillomas developed in addition at age 8. Treatment with cytosine arabinoside produced no change in tumor growth; the patient did not receive radiotherapy until the appearance of tracheal and bronchial squamous cell carcinoma 15 yr following the initial diagnosis. Irradiation and systemic and topical chemotherapy were ineffective, and recurrent arterial compromise due to malignant tumor emboli was eventually fatal. The clinical course in this patient indicates that malignant change can occur in recurrent juvenile papillomatosis in the absence of prior radiotherapy. (27 refs)

79-2268 Stimulation of Resistance to Tumor Growth of Athymic Nude Mice Pretreated by Combined

Local Hyperthermia and X-Irradiation. (Eng) Yerushalmi, A. (Radiation Unit, Weizmann Inst. Science, POB 26, Rehovot, Israel); Weinstein, Y. *Cancer Res* 39(3): 1126-1128; 1979.

The contribution of T lymphocytes to the stimulation of resistance against local tumor growth in athymic nude mice of C57BL background pretreated with local hyperthermia (HT) + x-irradiation was studied. Animals were pretreated in the left hind leg by local HT (42.7 for 45 min or 44.5 C for 60 min) and/or local x-irradiation (800 R). Twenty-four hours posttreatment, the animals were inoculated im with 0.5×10^6 metastatic Lewis lung carcinoma cells. Half of the animals in each group were inoculated in the pretreated leg and half were inoculated in the contralateral untreated leg. The life-span of normal and nude mice pretreated by local HT + irradiation was increased 30%-45%. The increase in life-span was similar in animals inoculated in the pretreated leg or in the untreated leg. These results indicate that T lymphocytes are not involved in the protection against tumor growth. (18 refs)

- 79-2269 Characteristics of a Low-Molecular-Weight Factor Extracted from Mouse Tumors that Affects In Vitro Properties of Macrophages.** (Eng) Cheung, H. T. (Immunobiology Res. Center and Dept. Medical Microbiology, Univ. Wisconsin, Madison, WI, 53706); Cantarow, W. D.; Sundharadas, G. *Int J Cancer* 23(3): 344-352; 1979.

The characteristics of a dialyzable low-mol-wt factor extracted from four different induced and spontaneous mouse tumors were studied. In the presence of the dialyzates derived from tumors, macrophages reversed their spreading and reverted to a round morphology. The effect was reversible, and the dialyzates had no apparent sublethal effects on the macrophages. The tumor dialyzates enhanced the migration of complete Freund's adjuvant-induced peritoneal cells out of capillary tubes. The migration of purified macrophages was similarly enhanced. Sodium azide (1 mM) inhibited the migration enhancement by approx 50% without affecting cell viability. The tumor dialyzates significantly inhibited the lipopolysaccharide-induced cytotoxicity of macrophages in a concentration-dependent fashion. Dialyzates from normal tissues had none of the foregoing effects. The macrophage-modulating factor in the tumor dialyzates was shown to be a product and property of the tumor cells per se, and not the tissues surrounding them. Partially purified factor, which retained all of the foregoing effects on macrophages, was not sensitive to heating, pronase, or a mixture of bovine spleen phosphodiesterase II, *Escherichia coli* alkaline phosphatase, and pancreatic ribonuclease. It was lipidlike and soluble in both organic solvents and aqueous media. It had ionizable group(s) and was anionic at neutral pH but nonionic under acid conditions. (27 refs)

- 79-2270 Enhancement of Tumor Outgrowth by Tumor-associated Blocking Factors.** (Eng) Hellstrom, K. E. (Div. Tumor Immunology, Fred Hutchinson Cancer Res. Center, Seattle, WA); Hellstrom, I. *Int J Cancer* 23(3): 366-373; 1979.

The ability of cell-free tumor fluid (TF) from 3-methylcholanthrene-induced BALB/c sarcomas to block antitumor immunity in vitro and to enhance tumor growth in vivo was studied. TF from two sarcomas, 1315 and 1321, decreased the in vitro cytotoxic effect of lymph node cells from tumor-immune, syngeneic donors (BALB/c mice), the blocking activity of these TF being greater than that of sera from tumor-bearing mice. Similar results were obtained with TF from sarcomas 1407 and 1408. The blocking activity was tumor line-specific. TF from sarcomas 1407 or 1408 nonspecifically enhanced the outgrowth of sarcomas 1407 and 1408 inoculated into syngeneic mice. There was also some degree of tumor line-specific enhancement. TF mixed directly with the inoculated tumor cells generally facilitated tumor outgrowth more than did TF given ip. TF prepared from normal spleen tissue did not cause a specific enhancement of 1407 outgrowth. TF from sarcomas 1321 and 1410 also enhanced 1321 and 1410 sarcoma outgrowth, with TF from the same

tumor enhancing slightly better than that from a different tumor. TF from sarcomas 1315 and 1321 given ip inhibited the growth of both sarcomas in vivo. (21 refs)

- 79-2271 Incapacity of Hematopoietic Stem Cell-deprived Mice to Produce Tumor Colonies Induced by Friend Virus-infected Cells.** (Eng) Wendling, F. (I.N.S.E.R.M. U.22, Institut du Radium, Batiment 110, Faculte des Sciences Paris-Sud, 91405 Orsay, France); Tambourin, P.; Moreau-Gachelin, F. *Exp Hematol* 6(10): 777-784; 1978.

The role of host hematopoietic stem cells in the formation of tumor colonies in the spleen of (C57BL/6 x DBA/2) F1 mice given grafts of spleen cells from polycythemia-inducing Friend virus (FVP)-infected DBA/2 donors was investigated. Hematopoietic stem cell compartments of recipient mice were destroyed by Myleran (busulfan) treatment or γ -ray irradiation. A single injection of Myleran (40 mg/kg, intragastrically) reduced the the number of pluripotent hematopoietic stem cells and erythropoietin-responsive cells (ERC) in polycythemic mice to around 1% of that of controls. Repeated injections of erythropoietin (EPO) restored the ERC population. Pretreatment of polycythemic hosts with Myleran totally suppressed the colony-forming ability of grafted FVP-infected spleen cells, but it had no effect on the colony-forming ability of grafted tumor cells isolated from a leukemic DBA/2 mouse 43 days after FVP infections. When Myleran-treated recipients were inoculated with EPO, spleen colonies were formed, and the number of colonies formed was similar to that in control mice. Similar results were obtained in hosts whose ERC populations were damaged by irradiation. These data strongly suggest that spleen colonies result from the proliferation of host cells transformed by virus released by FVP-infected cells and not from the proliferation of donor tumor cells. (29 refs)

- 79-2272 Natural Cytotoxicity--An Analysis of Effector Cells. The Role of the Fc Receptors.** (Eng) Kristensen, E. (Fibiger Lab., Ndr. Frihavnsgeade 70, DK-2100 Copenhagen O, Denmark); Langvad, E. *Cancer Immunol Immunother* 5(2): 71-76; 1978.

The microcytotoxicity assay was used to examine lymphocyte subpopulations derived from healthy donors and persons suffering from nonmalignant diseases for natural cytotoxicity (NC). Non-T lymphocytes exerted a significantly greater cytotoxicity against the established melanoma line RPMI 7931 than did T lymphocytes. The cytotoxicity of the non-T lymphocytes was dependent on the lymphocyte/target cell ratio. Both T and non-T lymphocytes showed little NC toward short-term target cell cultures. The cytotoxicity of non-T lymphocytes was enhanced by enrichment with Fc receptor-bearing (Fc R-positive) cells and reduced by depletion of R-positive cells; these cells above showed a high level

of NC. IgG split products, comprising the Fc portion of the molecule, and IgG immune complexes decreased the NC of Fc R-bearing non-T cells. The cells responsible for the increase in NC of T cells treated with IgG split products were associated with the Fc R-negative fraction. Monocytes contaminating the T-lymphocyte fraction were not involved in enhanced T-cell cytotoxicity. The F(ab')₂ immunoglobulin fragments had no effect on NC. The data indicate that most NC is expressed by cells belonging to the Fc R-bearing non-T fraction. (23 refs)

79-2273 A Specific Helper Factor Which Enhances the Cytotoxic Response to a Syngeneic Tumour.

(Eng) Kilburn, D. G. (Dept. Microbiology, Univ. British Columbia, Vancouver, British Columbia, Canada V6T 1W5); Talbot, F. O.; Teh, H. S.; Levy, J. G. *Nature* 277(5696): 474-476; 1979.

The isolation of a helper factor that specifically enhances the generation of cytotoxic cells in a syngeneic mouse tumor system is reported. The helper factor was prepared from a single splenic fraction obtained from 8-day tumor-bearing mice. The generation of cytotoxicity to syngeneic P815 mastocytoma cells was enhanced markedly at a concentration of 0.005 to 0.05 spleen equivalents. In addition, the purified factor increased the cytotoxicity of a normal (control) factor about fourfold in terms of cytotoxic units. The factor was specific for the syngeneic tumor system and was T-cell-dependent. It was coded for by the I region of the major histocompatibility complex and it bound antigen. However, although it bore I-region-coded markers, it did not possess constant-region determinants of mouse immunoglobulin. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of iodinated factor indicated that it is a monomer with a mol wt of 65,000. This factor may offer a means of altering tumor growth in vivo. (17 refs)

79-2274 Phytohaemagglutinin (PHA)-induced Cytotoxicity. II: The Effect of PHA-Stimulated Spleen Cells on Ehrlich Ascites Tumor Cells in Mice. (Jpn) Aoki, S. (Dept. Urology, Sch. Medicine, Keio Univ., Tokyo, Japan). *Jpn J Urol* 69(11): 1404-1411; 1978.

The effect of phytohemagglutinin (PHA)-stimulated mouse spleen cells on Ehrlich ascites tumor (EAT) cells was studied in ddY mice. The ³H-thymidine uptake of the spleen cells was enhanced by PHA stimulation (ratio of stimulated:unstimulated uptake was 27.5), as was the cytotoxicity (⁵¹Cr-release assay) of the spleen cells to the EAT cells (mean value at an effector/target cell ratio of 100:1 was 9.72%). Administration of PHA-stimulated spleen cells and EAT cells to the mice ip or sc produced antitumor effects. With the sc route, the tumor incidence was 1/4, vs 4/4 for mice inoculated with tumor cells alone and 4/4 for mice inoculated with tumor cells and untreated spleen cells from tumor-bearing

ers. The high rate of tumor formation in mice inoculated with the latter suggests the presence of suppressor T cells. Treatment by the ip route was accompanied by marked inflammatory changes of the visceral peritoneum that may have been induced by chemical mediators formed in the tumor-lymphocyte reaction. (31 refs)

79-2275 Phytohemagglutinin (PHA)-induced Cytotoxicity. III: Cell-mediated Immunoresponsiveness in Genitourinary Cancer Patients. (Jpn) Aoki, S. (Dept. Urology, Sch. Medicine, Keio Univ., Tokyo, Japan). *Jpn J Urol* 69(11): 1412-1421; 1978.

The phytohemagglutinin (PHA)-induced cytotoxicity of the peripheral blood lymphocytes (PBL) from 32 genitourinary cancer patients and 13 normal subjects against HeLa cells was compared. Among the patients there were 9 cases of bladder cancer, 6 prostatic carcinomas, 5 renal cell carcinomas, 4 renal pelvic tumors, 3 testicular carcinomas, 2 ureteral tumors, 2 uterine carcinomas, and 1 urethral carcinoma. The PHA-induced cytotoxicity of the patient PBL was decreased significantly compared with that of the control PBL, especially in patients with advanced renal cell carcinoma. Periodic tests of all patients showed that cytotoxicity decreased as the cancer progressed. The degree of PHA-induced blastoid transformation of the patient PBL was also reduced, and it correlated with the PHA-induced cytotoxicity. In addition, the number of PBL was decreased in the patients. However, this decrease plus the high RBC sedimentation rate value and the high α_1 -globulin, α_2 -globulin, and fibrinogen levels found in this group did not significantly correlate with the decreased PHA-induced cytotoxicity and blastoid transformation of their PBL. (41 refs)

79-2276 Is Antibody-dependent Cellular Cytotoxicity an Important Mechanism of Resistance to Tumors In Vivo? (Eng) Cavallo, G. (Istituto di Microbiologia, Univ. Torino, Via Santena 9, 10126 Turin, Italy); Giovarelli, M.; Forni, G.; Landolfo, S. *Immunochimistry* 15(10/11): 801-805; 1978.

The effect of passive administration of heterologous antibody before tumor challenge was investigated in adult and newborn BALB/c mice. Adult mice preinjected once or twice with absorbed rabbit antibody to mammary adenocarcinoma ADK-1t IgG showed a decrease in ADK-1t tumor takes of 60% and 80%, respectively, compared with controls preinjected with absorbed normal rabbit IgG. In newborn mice, heterologous antibody treatment resulted in only an initial delay of tumor growth, and there was no significant difference in final tumor incidence. No differences in tumor growth and final incidence were observed in mice preinoculated with normal or ADK-1t immune rabbit IgG and challenged with sarcoma cells. The absorbed antibody showed a single precipitation band in agar gel. It is concluded that the pres-

ence in the first phases of the tumor-host relationship of heterologous tumor-specific antibody can drastically enhance host resistance to a spontaneous, poorly immunogenic tumor. The antibody activity appears to be mediated by complex interactions with the multifactorial system of host reactive mechanisms. The results of this and other studies suggest that anti-tumor-specific humoral antibody might constitute a potent tool in the immunotherapy of neoplasia. (31 refs)

- 79-2277 Differences in Antibody Fixation on SV40-transformed Cells in the Presence and Absence of Complement.** (Fre) Duthu, A. (Laboratoire d'Immunochimie virale, Institut de Recherches Scientifiques sur le Cancer, B.P. No. 8, F94800 Villejuif, France); de Vaux Saint Cyr, C. *Bull Cancer (Paris)* 66(1): 17-24; 1979.

The fixation of antibodies directed against virus-induced antigens on simian virus 40-transformed Syrian hamster fibroblasts (TSV,Cl₂) was studied during incubation of the cells in sera from tumor-bearing hamsters in the presence or absence of guinea pig complement. Antibody fixation was revealed by an anti-hamster immunoglobulin immune serum labeled with ¹²⁵I. Autoradiographic observations were made by light and electron microscopy. Cells incubated with antibodies alone were labeled evenly on the plasma membrane, and there was no decrease in total cell population compared with controls. When the cells were incubated in complement-containing sera, one cell subpopulation was labeled heavily, and these cells detached from the flask and were destroyed. After 11 hr of incubation, about one-fifth of the cells still attached to the flask were labeled heavily, but the others were not labeled. The findings indicate the protective action of antibodies toward tumor cells when complement is absent or inactive in vivo. (23 refs)

- 79-2278 Genetic Control of Responsiveness to the Tumor-associated Transplantation Antigen of a Chemically Induced Murine Fibrosarcoma.** (Eng) Parmiani, G. (Div. Experimental Oncology A, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via G. Venezian 1, 20133 Milano, Italy). *Immunogenetics* 7(3): 271-275; 1978.

A possible genetic basis for strain differences in the immune response to a methylcholanthrene-induced transplantable fibrosarcoma (C-1) was investigated in hybrid mice. BALB/c/Dp (C) females, which were not resistant to the tumor and carried the *H-2k* haplotype, were bred to unresponsive BALB/c x C3Hf/Dp (CC3) males, which carried the *H-2d* haplotype. On challenge with 10⁵ C-1 cells, 18/22 mice with the *H-2d/d* haplotype were tumor-resistant, whereas 18/20 mice with the *H-2d/d* haplotype developed tumors. Immunity to the individual tumor-associated transplantation antigens (TATA) of C-1 was found predominantly among mice with the *H-2d/k* genotype. Hy-

brids between C and the congenic BALB.B (*H-2b*) mice developed anti-TATA immunity. Hybrids between C mice and recombinant strains of background A (which contained different subregions of the *H-2k* haplotype) showed 34%-94% protection against tumor challenge. The results indicate a genetic control over in vivo immunity to the individual TATA of C-1. The control appears to be polygenic, in that both the dominant gene(s) mapping in the I region of the major histocompatibility complex (MHC) and apparently governing the unresponsive trait, as well as non-H-2 genes, which possibly counteract the effect of the MHC gene(s), seem to be involved. (14 refs)

- 79-2279 Transplantability of Ferridextran-induced LEW/CUB Tumours, FLA, FLB, FLC, and FL.** (Eng) Kren, V. (Dept. Biology, Faculty General Medicine, Charles Univ., Prague, Czechoslovakia); Kršáková, M.; Bila, V. *Folia Biol (Praha)* 24(6): 389-390; 1978.

The transplantability of four ferridextran-induced tumors (FL, FLA, FLB, and FLC) was examined in syngeneic LEW recipients and in LEW congenic hybrids. In the syngeneic animals, the transplantability of the four tumors was almost 100%. In the congenic hybrids, the only tumor to cross the H-1 barrier was FLB, which killed a female LEW.1A x LEW.1D recipient. However, the FLA and FLB tumors killed 100% of intact H-4 and H-5 congenic recipients, ie, LEW.C-4A and LEW.1x-5P. The FLC tumor killed 11/12 LEW.C-4A recipients but only 11/24 LEW.1x-5P recipients. Although FLA, FLB, and FLC were all rejected by LEW.C-4A recipients primed with FL tumor cells, the tumors killed, respectively, 19/23, 8/22, and 4/17 primed LEW.1x-5P recipients. It is suggested that the differences in cell surface properties of tumors could be responsible for their different abilities to cross some alloantigenic barrier or to be rejected. (5 refs)

- 79-2280 Determination of Plasma Levels of Carcinoembryonic Antigen by Two Methods.** (Jpm) Murata, K. (Central Clinical Lab., Kansai Medical Univ. Hosp., Kansai, Japan); Fujiwara, H.; Kan, Y. *Gan No Rinsho* 25(2): 107-114; 1979.

The determination of plasma levels of carcinoembryonic antigen (CEA) by the double antibody (DA) method and the solid phase (SP) method was compared. The DA method was superior with respect to reproducibility, stability after long-term freeze storage, and accuracy. The average recovery values were 102.3% for the DA method and 78.5% for the SP method. However, the DA method was more complicated and less convenient than the SP method. In normal subjects, the CEA levels were found to be < 10 nanograms (ng)/ml. Six patients with cancers at various sites had levels > 10 ng/ml; patients with benign tumors also had abnormally high levels of CEA. (10 refs)

- 79-2281 The Immune Response of (C57BL/6 x C3H)F₁ Mice to the Endogenous AKR-MuLV.** (Eng) Ihle, J. N. (Basic Res. Program, NCI Frederick Cancer Res. Center, Frederick, MD, 21501); Lee, J. C. *Med Microbiol Immunol (Berl)* 164(1/3): 207-216; 1977.

The humoral and cellular immune response of (C57BL/6 x C3H)F₁ mice to the endogenous AKR murine leukemia virus (MuLV) was characterized. The data clearly indicated the existence of an intact immune response against the virus. Antibodies specifically directed against the envelope glycoprotein gp71 and the envelope protein component p15(E) were present in all mice after 3 mo of age, and they constituted a chronic lifelong immune response. The antibody against gp71 was type-specific, and the IgG antibodies could mediate complement-independent neutralization of virus infectivity. The antibodies against p15(E) were group-specific and did not neutralize virus infectivity. Spleen cells from 6-wk-old mice were specifically cytotoxic against an AKR MuLV-producing tumor cell line but not against two nonproducing fibroblast cell lines. This cytotoxicity could be blocked with AKR MuLV gp71 or intact virus, but not with Rauscher leukemia virus (RLV) gp71 or RLV. Killing was shown to be mediated by null cells and by T cells capable of responding to gp71 in vivo and of being induced in vitro. In experiments designed to assess the consequences of the expression of endogenous viral antigens, the growth of virus-positive tumors in immune-positive mice was significantly less than that of virus-negative tumors in either immune-positive or -negative mice. These data suggest that the coupled expression of viral antigens with transformation in immune-responsive mice may actually contribute to tumor regression. (17 refs)

- 79-2282 Microenvironmental Influences on Granulopoiesis in Acute Myeloid Leukemia.** (Eng) Greenberg, P. (Dept. Medicine, Veterans Adm. Hosp., Palo Alto, CA, 94304); Mara, B. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book A), 528 pp.; 405-409; 1978.

Marrow cell-derived colony-stimulating activity (CSA) levels in normal subjects and in patients with acute myeloid leukemia (AML) were assayed. In normal subjects, all of the CSA was provided by the adherent cell population. It was found that 84%-87% of the adherent marrow CSA-producing cells were α -naphthyl acetate esterase positive, resembled monocytes morphologically and were capable of phagocytosing latex particles. This suggests that middensity monocytes and macrophages contribute a major portion of the marrow CSA. Thirteen of 21 patients with AML had significantly low marrow CSA levels at diagnosis or relapse. Only 4/13 patients with low marrow CSA entered complete remission, whereas 7/8 patients with normal CSA did. Four patients in partial remission and 42/46 in complete remission had normal marrow CSA values. In contrast, low or progressively decreasing marrow CSA values occurred in patients with impending relapse. Marrow CSA values paralleled marrow granulocytic progenitor cells (colony-forming units--culture,

CFU-C) during remission until relapse, with normal CSA values persisting longer than CFU-C. The monitoring of marrow CSA provision appears useful for evaluating microenvironmental influences and intramedullary cellular interactions on granulopoiesis and for assessing prognosis and clinical status in AML. (30 refs)

- 79-2283 Introduction.** (Eng) Lennert, K. (Dept. General Pathology and Pathologic Anatomy, Univ. Kiel, Kiel, W. Germany). *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 807-809; 1978.

A section of the Cold Spring Harbor Conference on Cell Proliferation concerning malignant lymphomas is introduced. The hematopoietic stem cell gives rise to many variants of T and B lymphocytes that are separated according to differentiation and function and defined by their morphology and immunologic markers. Each type of cell may be involved in one or more types of malignant lymphoma. Every tumor is derived from B or T cells or is not identifiable as B- or T-cell derived (null cell lymphoma). (2 refs)

- 79-2284 An Immunologic Approach to Classification of Malignant Lymphomas: A Cytokinetic Model of Lymphoid Neoplasia.** (Eng) Lukes, R. J. (Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033); Lincoln, T. L.; Parker, J. W.; Alavaikko, M. J. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; pp. 935-952; 1978.

The immunologic approach of the Lukes-Collins (L-C) classification of malignant lymphomas (ML), which relates their morphologic features to findings of modern immunology, is described. In this approach lymphoma cells are regarded as defective immune cells that frequently arise in abnormal immune processes and migrate, target, and function in a manner similar to that of their normal counterparts. The classification is based on the concepts that ML principally involve the T-, B-, and undefined (U)-cell systems and that they commonly develop as a block or switch-on (derepression) of lymphocyte transformation. Because the L-C classification follows the transformation sequence of T and B cells, particularly follicular center cells, it lends itself to cell kinetics studies. Preliminary studies of representative non-Hodgkin's lymphomas, in which both flow cytometry and microfluorometry were used, demonstrated a relationship between cell size, DNA content, and cycle time. The L-C classification led to characteristic DNA-content curves for specific tumor cell populations. The lymphoma cells were demonstrated to be hyperdiploid in DNA content, a finding that, in the future, may allow active benign proliferations to be distinguished from malignant ones. (28 refs)

- 79-2285 Analysis of the Biosynthesis of T25 (Thy-1) in Mutant Lymphoma Cells: A Model for Plasma Membrane Glycoprotein Biosynthesis.** (Eng) Hyman, R. (Dept. Cancer Biology, Salk Inst. Biological Studies, San Diego, CA, 92112); Trowbridge, I. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 741-754; 1978.

Techniques for isolating mutant murine lymphoma cells that show specific defects in the expression of a membrane protein (T25) that carries the Thy-1 alloantigenic determinant are reviewed. Thy-1 mutants have been isolated primarily by cytotoxic immunoselection against allospecificity on cloned Thy-1+ tissue culture-adapted lymphomas. All of the mutants show concomitant loss of the entire T25 molecule from the cell surface. Five complementation classes have been identified; four of them (A, B, C, and E) probably have defects in genes other than the structural gene coding for the Thy-1 alloantigenic difference. The defect in the class-D mutant, however, is in the structural gene coding for the Thy-1 alloantigenic specificity. Biosynthetic labeling experiments demonstrated that all complementation classes except class D synthesize an altered T25 molecule. Pulse-chase experiments and electron microscopy showed that T25 accumulates inside the mutant cells instead of reaching the cell surface and is subsequently degraded. Glycopeptides from T25 molecules of classes A, C, and E mutants do not contain the complex of oligosaccharides found on wild-type cells. In addition, the simple oligosaccharides of the T25 glycoprotein in the class E mutant are smaller than those of the T25 glycoproteins of the other mutants and the wild-type cells. Studies of the expression of Thy-1 in lectin-resistant lines support the hypothesis that defects in the biosynthesis of the oligosaccharide units of T25 can cause the loss of Thy-1 expression on the cell surface. (65 refs)

- 79-2286 Incidence and Pathological Features of Spontaneous Tumors in Athymic Nude Mice.** (Eng) Sharkey, F. E. (Dept. Pathology, Milton S. Hershey Medical Center of Pennsylvania State Univ., Hershey, PA, 17033); Fogh, J. *Cancer Res* 39(3): 833-839; 1979.

The incidence of histopathological features of spontaneous tumors arising in 1,141 athymic nude mice over a 26-mo period were studied. Twenty-four spontaneous tumors (2.1%) were identified, 22 of them arising in the 324 mice that survived for 5 mo or more. Eighteen of the tumors were of the lymphoma-leukemia variety, with six tumors corresponding to Dunn's reticulum cell neoplasm type A. Transplantation of the spontaneous tumors to other nude mice was successful in 3/5 cases. Mice receiving transplants of human colon adenocarcinomas or urogenital tumors developed spontaneous tumors more often than did mice receiving other human tumor transplants. Progressive growth of the human tumor transplants occurred significantly less often in the mice that eventually developed spontaneous tumors than in the mice that showed no spontaneous tumor development. Nevertheless, the incidence of spontaneous tumors in these

mice was similar to that reported for the thymus-bearing Swiss background strain. (16 refs)

- 79-2287 The Evolution of Immunoblastic Lymphomas in Morphologically Nonneoplastic Immunoproliferative Diseases.** (Eng) Rappaport, H. (Dept. Anatomic Pathology, City of Hope Natl. Medical Center, Duarte, CA, 91010); Pangalis, G. A.; Nathwani, B. N. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 877-895; 1978.

The development of malignant lymphoma in two initially nonneoplastic immunoproliferative disorders, intestinal α -chain disease (α -CD) and angioimmunoblastic lymphadenopathy (AILD), is reported. The immunoperoxidase technique was applied to fixed-tissue sections of three cases of intestinal α -CD. Both the plasma cells of the diffuse infiltration and the tumor immunoblasts were strongly positive for α -chains and negative for other chains tested. Forty-two patients with AILD were compared with 36 patients with AILD plus immunoblastic lymphoma (AILD + IL). Patients with AILD tended to respond better to prednisone or to chemotherapeutic agents than patients with AILD + IL. Complete remissions occurred in 63% of the AILD patients, vs 26% of the AILD + IL patients. The median survival was longer for patients with AILD. Malignant lymphoma was evident at autopsy in 20% of the patients with AILD group and 82% of those with AILD + IL; and extranodal involvement by malignant lymphoma at autopsy was observed much more often in the AILD + IL cases. The results indicated that malignant lymphoma can develop in AILD patients after latent periods of unpredictable duration. In AILD, the observations suggest a process of dedifferentiation, since the neoplastic immunoblasts have a diminished capacity for forming immunoglobulins. (47 refs)

- 79-2288 Membrane Phenotypes of Human Leukemic Cells and Leukemic Cell Lines: Clinical Correlates and Biological Implications.** (Eng) Greaves, M. (Membrane Immunology Lab., Imperial Cancer Res. Fund Labs., Lincoln's Inn Fields, London WC2A 3PX, England); Janossy, G.; Francis, G.; Minowada, J. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 823-841; 1978.

Results of screening 1,000 untreated or relapsed cases of leukemia and a substantial number of treated cases with newly developed antisera to acute lymphoblastic leukemia (ALL) are reported. The anti-ALL were applied in parallel with a panel of differentiation-linked membrane markers and two enzymes, terminal deoxynucleotidyl transferase (TdT) and hexosaminidase isoenzyme (Hex). Anti-ALL antibodies reacted with leukemic cells from a proportion (but not all) of patients in three groups: ALL, acute undifferentiated leukemia, and Ph¹-chromosome-positive chronic myelocytic leu-

kemia (CML) in blast crisis. In ALL, strong positivity with anti-ALL was restricted to those patients whose leukemic cells were unreactive with T- and B-lymphocyte markers, ie, null-type (non-T, non-B) ALL. Using anti-ALL and other membrane markers, acute leukemias were dissected into several subclasses that have prognostic significance. The major division within ALL is between the groups designated Thy-ALL and common ALL, which have substantially different prognoses. In a group of > 90 leukemic children followed for up to 4 yr, positive reactions with anti-ALL identified a major subgroup of ALL that has a highly favorable prognosis. In a series of 26 adult anti-ALL-positive patients followed for 2 yr, 2 relapsed: in 1 of these, reemerging leukemic cells were detected immunologically 2 mo ahead of clinical and hematological relapse. It is suspected that both ALL and Ia-like antigens, as well as TdT, are normal gene products of the target cells for acute leukemia transformation and that they may play an important role in early (normal) hematopoiesis. (56 refs)

- 79-2289 Hodgkin's Disease and Anergy.** (Eng) Shifan, T. A. (Div. Hematology and Oncology, Dept. Medicine T-006, Univ. California, San Diego, La Jolla, CA, 92093); Mendelsohn, J. *Blut* 38(1): 1-7; 1979.

A new hypothesis for the pathogenesis of Hodgkin's disease based on the clinical, histologic, and immunologic features of the disease is presented. According to this hypothesis, viral infection of a lymph node cell leads to a vigorous but ineffective immune response. The virus-transformed cells then proliferate and antigenically stimulate the immune system. Host T cells are activated to proliferate, resulting in lymphokine production, B-cell activation leading to immunoglobulin synthesis, and transient regulatory suppression of T-cell activation by other antigens. Specific cellular cytotoxicity to the transformed cells is ineffective, allowing the transformed cells to remain viable and to continue to provide antigenic stimulation. The result is chronic lymphokine production and, in turn, pleomorphic infiltration of proliferating reactive lymphocytes, plasma cells, eosinophils, and macrophages around the transformed infected cells. B-cell activation might also persist with chronic stimulation, and thus occasional hypergammaglobulinemia may develop. The chronic antigenic stimulation leads to chronic rather than transient suppression of the immune response to other antigens, resulting in clinical anergy. Genetic factors might also play a role in the cellular immune response. (29 refs)

- 79-2290 Tumor Acceptance Modified by Passage in Hybrids with Graft-Versus-Host Reaction.** (Eng) Jacobs, B. B. (Life Sciences Center, Nova Univ., 3301 College Ave., Fort Lauderdale, FL, 33314); Parks, R. C. *Exp Hematol* 6(10): 785-790; 1978.

A graft-vs-host reaction (GVHR) was produced in adult F₁

hybrids of DBA/1 (D1), BALB/c (C), and C57BL/6 (B6) mice by an injection of 10⁶ parental strain spleen cells; and 8 days later, the hybrids were challenged with an allogeneic third-party tumor. The BALB/c Leydig cell tumor C4092, the C57BL/6 sarcoma 30795, and the DBA/1 melanoma S91 often grew progressively in B6D1F₁, CD1F₁, and B6CF₁ hybrids or their reciprocal hybrid recipients, respectively, when a GVHR had been induced in these animals. Control hybrids without a GVHR always rejected the tumor. The C4092 tumor was serially transplantable in untreated hybrids after its initial passage in unrelated GVHR-treated mice; the S91 tumor grew in its first passage into untreated B6CF₁ mice but thereafter was rejected by these hybrids; the B6 tumor 30795 grew progressively only in the initial GVHR-treated CD1F₁ or reciprocal hybrids. The reduced immunogenicity of tumors resulting from their passage in unrelated recipients immunosuppressed as a result of a GVHR is comparable to allograft adaptation achieved by techniques such as organ culture pretreatment and presents an additional method for attenuating the rejection of allotransplants. (24 refs)

- 79-2291 Kaposi's Sarcoma in Organ Transplant Recipients. Report of 20 Cases.** (Eng) Penn, I. (Dept. Surgery, Univ. Colorado Sch. Medicine, Denver, CO, 80220). *Transplantation* 27(1): 8-11; 1979.

The incidence of Kaposi's sarcoma (KS) among organ transplant recipients is reported. Among 604 recipients who developed 630 de novo malignancies after transplantation, 20 developed KS. All 20 had received renal transplants from malignancy-free donors. Among the general population of the US, KS comprises only 0.6% of all cancers. The average of the recipient KS patients was 42 yr at the time of transplantation, and KS appeared an average of 16 mo after transplantation. In contrast to the general heavy male preponderance of KS, the male:female ratio in this series was only 2.3:1. All patients had been treated with substantial quantities of immunosuppressive drugs, and 11 had received local radiation therapy to the homograft. At least six patients had had herpes simplex virus infections prior to the appearance of KS. One KS recipient also developed a reticulum cell sarcoma of the brain and another developed a carcinoma in a colonic polyp. Eleven of the patients had benign KS, and nine had the malignant variety with involvement of the internal viscera. Four of the 11 patients with benign lesions died from infection and 8/9 patients with malignant disease died from the malignancy. (20 refs)

- 79-2292 Immunological Investigations of Carcinoma of the Cervix.** (Eng) Tilz, G. P. (Medizinische Universitätsklinik, Auerbruggerplatz, A-8036, Graz, Austria); Buffe, D.; Rimbaut, C.; Pickel, H. In: *Cervical Pathology and Colposcopy. Selected Papers from the Second World Congress of Cervical Pathology and Colposcopy held in Graz, Austria, 15-18 October 1975*. Burghardt, E.; Holzer, E.; Jordan, J. A.,

eds. (Stuttgart: Georg Thieme Publishers): 146 pp.; 88-97; 1978.

Immunological testing was performed on first-admission patients with cervical carcinoma before any form of treatment was initiated. No evidence of tumor-specific antigen was found. Patients with advanced cervical carcinoma were immunodepressed, and the degree of immunosuppression correlated with the stage of the disease. Studies of tumor-associated antigens showed no correlation of α_1 -fetoprotein with carcinoma of the cervix. The tumor-associated antigen α_1 -H-globulin correlated well with the evolution of malignancy and seems to be a very useful tool for following patients under treatment. Modification of serum proteins was less impressive than that observed in gastrointestinal lesions and consisted of a diminution of albumin and the esterases and an increase of IgA, ceruloplasmin, and the slow-migrating lipoproteins. Amino acid mapping analyses showed that amino acid levels increased as the cervical carcinoma progressed in nearly all cases. Leucine was particularly prominent. (28 refs)

- 79-2293 HLA and Testicular Cancer.** (Eng) DeWolf, W. C. (Sidney Farber Cancer Inst., Harvard Medical Sch., Boston, MA, 02115); Lange, P. H.; Einarson, M. E.; Yunis, E. J. *Nature* 277(5693): 216-217; 1979.

Tissue typing results are presented for 61 patients with testicular cancer. Thirty patients had seminoma, 27 embryonal cell carcinoma, 26 teratocarcinoma, and 7 choriocarcinoma.

All patients had completed treatment and were clinically free of disease at the time of testing. The antigen frequency of the human major histocompatibility complex (HLA) determinant Dw7 (HLA-Dw7) was significantly increased in the teratocarcinoma group (12/26) compared with that in normal controls (14/150). This difference was not detected in the other patient groups or in the group as a whole. The association between HLA and testicular teratocarcinoma is of interest considering the homology between the major histocompatibility complex of the mouse (H-2) and HLA and the relationship between teratocarcinoma and H-2 in the mouse. (18 refs)

See also:

- *(Rev.): 79-1801, 79-1802, 79-1818, 79-1834, 79-1839, 79-1845, 79-1846, 79-1847, 79-1848, 79-1849, 79-1850, 79-1851, 79-1852, 79-1853, 79-1855, 79-1856, 79-1864, 79-1865, 79-1885, 79-1889.
- *(Chem.): 79-1905, 79-1909, 79-1927, 79-1934, 79-1974, 79-2031, 79-2038, 79-2068.
- *(Phys.): 79-2105, 79-2117, 79-2122, 79-2123.
- *(Viral): 79-2138, 79-2147, 79-2151, 79-2155, 79-2162, 79-2167, 79-2173, 79-2179, 79-2181, 79-2188, 79-2190, 79-2192, 79-2194, 79-2196, 79-2212, 79-2216.
- *(Path.): 79-2300, 79-2304, 79-2325.

PATHOGENESIS

79-2294 Translocation 8;14 in an Ataxia Telangiectasia-derived Cell Line. (Eng) Jean, P. (Laboratoire de cytogénétique, Département d'anatomie, Université de Montréal, Montréal, Canada H3C 3JC); Richer, C. L.; Murer-Orlando, M.; Luu, D. H.; Joncas, J. H. *Nature* 277(5691): 56-58; 1979.

Phytohemagglutinin-stimulated peripheral blood lymphocytes from a 17-yr-old boy with ataxia telangiectasia (AT), a cell line (CB-1) established from his blood lymphocytes and transformed in vitro with Epstein-Barr virus (EBV), a cell line derived from normal cord blood transformed by EBV (Cb 8-11), and a Burkitt's lymphoma (BL)-derived cell line were analyzed by R banding. No significant chromosomal abnormalities were observed in the metaphases from the peripheral blood WBC of the AT patient. However, the CB-1 line showed three different abnormalities, the first two of which were present in all metaphases examined: a translocation t(8q; 14q+), a metacentric marker the size of an X chromosome with a large dark band just above the centromere, and a trisomy 21. The first two abnormalities closely resembled those seen in BL-derived cell lines, BL tumor cells, and other lymphomatous cells. In the control cell line Cb 8-11, chromosomes 8, 14, and 21 were normal, and no metacentric marker was seen. Although the AT patient had no features of the trisomy 21 syndrome, two first-degree cousins of his father had children with Down's syndrome. It appears that the addition of EBV to the apparently normal lymphocytes of an AT patient revealed either a quiescent clone or an increased chromosome fragility. (17 refs)

79-2295 Correlation of a Specific Chromosomal Marker, 21q-, and Retroviral Indicators in Patients with Thrombocythemia. (Eng) Fuscaldo, K. E. (Dept. Medical Oncology and Hematology, Herbert L. Orlovitz Inst. Cancer and Blood Diseases, Hahnemann Medical Coll. and Hosp., Philadelphia, PA); Erlick, B. J.; Fuscaldo, A. A.; Brodsky, I.; Zaccaria, A. *Cancer Lett* 6(1): 51-56; 1979.

Thirty-eight patients with myeloproliferative disorders (MPD), including polycythemia vera, essential thrombocythemia, chronic myelocytic leukemia, and acute nonlymphocytic leukemia, were evaluated in Philadelphia (30 patients) and in Bologna, Italy (8 patients), for the presence of chromosomal markers. Twenty-eight patients were positive for the chromosomal anomaly 21q- and eight were negative. The 30 Philadelphia patients were evaluated for the presence of RNA-directed DNA-polymerase (RDDP) which is indica-

tive of retroviral activity. Sixteen patients were positive for RDDP and five were negative. There was a positive correlation between the presence of viral and chromosomal markers. Viral indicators were not found in platelet material when the 21q- deletion in dividing bone marrow cells was absent. The identification of a specific chromosomal marker, 21q-, may be important in understanding the etiology of these MPD. The fact that viral particles were detected only in cells with a deletion of the long arm of chromosome 21 may indicate an enhanced expression of virus in those cells in which the antiviral effects of chromosome 21 were impaired. (16 refs)

79-2296 Myelofibrosis and Acute Lymphoblastic Leukemia in a Child with Down Syndrome. (Eng) Nordan, U. Z. (Div. Hematology, Dept. Pediatrics, State Univ. New York at Buffalo, Buffalo, NY); Humbert, J. R. *J Pediatr* 94(2): 253-255; 1979.

The case of an 8-yr-old girl with Down's syndrome who developed myelofibrosis with concurrent acute lymphoblastic leukemia is presented. Bone marrow aspiration showed scanty marrow tissue with 21% lymphoblasts and 9.5% monocytes. Bone marrow biopsy showed hypoplasia and myelofibrosis with increase marrow reticulin. Acute leukemia and myelofibrosis may reflect extreme examples of the disruption of bone marrow proliferation control mechanisms in Down's syndrome. (9 refs)

79-2297 Hairy Cell Leukemia-associated Familial Lymphoproliferative Disorder. Immunologic Abnormalities in Unaffected Family Members. (Eng) Cohen, H. J. (Medical Service, Veterans Adm. Hosp., 508 Fulton St., Durham, NC, 27705); Shimm, D.; Paris, S. A.; Buckley, C. E.; Kremer, W. B. *Ann Intern Med* 90(2): 174-179; 1979.

A family in which members of three generations were affected by hematologic malignancies was studied. The proband had hairy cell leukemia, a brother had chronic lymphocytic leukemia, the father had chronic myelogenous leukemia, and a nephew had a cutaneous and CNS lymphoma. The proband and his brother were HLA identical to a normal sister; the third affected family member with lymphoma shared no HLA antigens. There was no clinical evidence for immune deficiency in 17 unaffected family members, but several showed an abnormally low percentage of cells forming sheep RBC rosettes, suggesting a decrease in T-cell number and expansion of a null cell pool. Several family members also

showed an abnormally low response to phytohemagglutinin and concanavalin A as well as a markedly reduced cutaneous hypersensitivity reaction. When tested for complement-fixation viral antibody titers to commonly encountered viral antigens, family values were considerably below normal values for all antibodies except those to Cocksackie B4. The decreased immune function in these family members suggests a role for the immune system in the emergence of hairy cell leukemia and other lymphoid malignancies. (26 refs)

- 79-2298 Lymphoproliferative Disease in Two Sisters.** (Eng) Garrett, J. V. (Christie Hosp., Withington, Manchester M20 9BX, England); Newton, R. K. *Br Med J* 1(6158): 234-235; 1979.

The occurrence of chronic lymphatic leukemia (CLL)-type lymphocytosis in two sisters is reported. One sister, aged 82, had ordinary-type CLL. One of her three children had died of pancreatic carcinoma. The second sister, aged 75, had prolymphocytic leukemia. Of her four children, one had died of Still's disease and one of ovarian carcinoma. One of the sisters' six siblings had colon carcinoma; the others had unremarkable histories. The simultaneous occurrence of two forms of lymphoproliferative disease in two sisters seems likely to be associated with some inherited instability of the lymphocyte system. (4 refs)

- 79-2299 Congenital Agranulocytosis Terminating in Acute Myelomonocytic Leukemia.** (Eng) Rosen, R. B. (Dept. Pediatrics, City of Hope Medical Center, 1500 E. Duarte Rd., Duarte, CA, 91010); Kang, S. J. *J Pediatr* 94(3): 406-408; 1979.

The development of acute nonlymphocytic leukemia in a 14-yr-old boy with an infantile genetic agranulocytosis (IGA)-like disease is reported. The IGA-like disease was characterized by onset in infancy, recurrent infections, agranulocytosis, monocytosis, and deficiency of marrow neutrophil granulocytes beyond the myelocyte stage. A 9-yr-old sister had Down's syndrome. Over the years, the patient had received numerous antibiotics, including the possible leukemogen chloramphenicol. Cytogenetic studies were normal at the time of diagnosis of the leukemia. Although the possibility that the leukemia was a chance occurrence cannot be excluded, this case supports the classification of congenital agranulocytosis as a preleukemic state or a condition with a predilection to terminate in leukemia. (10 refs)

- 79-2300 Heterotransplantation of a Human Leukemic T-Cell Line in Hamsters.** (Jpn) Hiraki, S. (Dept. Second Internal Medicine, Okayama Univ. Medical Sch., Okayama, Japan); Miyoshi, I.; Nakamura, K.; Ohta, T.; Ikeda, H.; Tsubota, T.; Uno, J.; Tanaka, T.; Kimura, I. *Jpn*

J Clin Hematol 19(11): 1519-1522; 1978.

A leukemic T-cell line (TALL-1) from the bone marrow of a 28-yr-old man in the terminal stage of T-cell lymphosarcoma was recently established in permanent culture. The ip implantation of $1.8-2.9 \times 10^7$ TALL-1 cells in seven newborn Syrian hamsters treated with rabbit anti-hamster thymocyte serum gave rise to invasive tumors after 26-41 days. There was involvement of the parathymic lymph nodes, liver, gallbladder, brain, meninges, and uvea. The donor had widespread leukemic involvement, including the meninges and eyes, during his clinical course. This in vivo model system may be useful for studies of the characteristics of human T-cell leukemia-lymphoma. (10 refs)

- 79-2301 Membrane Markers in Human Lymphoid Malignancies: Clinicopathological Correlations and Insight into the Differentiation of Normal and Neoplastic Cells.** (Eng) Seligmann, M. (Lab. Immunochemistry and Immunopathology, Res. Inst. Blood Diseases, Hopital Saint-Louis, 75475 Paris Cedex 10, France); Preud'homme, J. L.; Brouet, J. C. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 859-876; 1978.

Immunologic and enzymatic markers in human lymphoid malignancies that are relevant to the clinicopathological pattern or to the differentiation of normal lymphoid cells were studied. In 167 untreated patients with acute lymphoblastic leukemias (ALL), B and T cells were present, respectively, in 10% and 25% of the patients; non-B, non-T cells were found in 65% of the patients. In 85% of the cases of T-derived ALL, most blast cells exhibited a strong acid phosphatase positivity with numerous granules in the Golgi area, but such positivity was found in < 10% of the non-T, non-B ALL cases. The following features were more often present in T-derived ALL than in non-B, non-T ALL: a tumoral presentation, a mediastinal mass, and high blast-cell blood counts. The incidence of continuous complete remission was higher in the non-T, non-B subgroup compared to the T subgroup. T-derived ALL had slightly lower mean terminal deoxynucleotidyl transferase activity, compared with the non-T, non-B group. Nineteen of 23 chronic lymphocytic leukemia (CLL) cases exhibited clinical and hematological features indicative of a T origin of the leukemia. The differentiation patterns of B-cell proliferations in the CLL cases are discussed. It is suggested that the proliferating cells may not necessarily represent the target cells for the neoplastic event and that, even when they appear to be frozen at a given stage of differentiation, the tumor cells may arise from a precursor cell. (73 refs)

- 79-2302 Genetic Control of Hemoglobin Production by Murine Erythroleukemic Cells.** (Eng) Skoultchi, A. I. (Dept. Cell Biology, Albert Einstein Coll. Medicine, Bronx, NY, 10461); Benoff, S.; Bruce, S. A.; Lin, P. F.; Lonial, H.; Pyati, J. *Cold Spring Harbor Conf Cell Proliferation*

Vol. 5(Book B), 994 pp.; 723-740; 1978.

Genetic control of Hb synthesis was studied in Friend murine erythroleukemic (EL) cells by cell hybridization and by the isolation and characterization of noninducible EL cells. A hypoxanthine-guanine phosphoribosyltransferase (HGPRT)-deficient EL cell line lacking a normal X chromosome was fused with mouse bone marrow cells and mouse lymphoma cells. Hb inducibility was demonstrated in hybrid lines in which most cells did not bear an X chromosome, whereas the lines that had retained an X chromosome were inhibited for Hb production. Karyological analysis failed to reveal a correlation between inhibition of inducibility and any chromosome other than the X chromosome. This finding was confirmed by measurements of HGPRT activity in cell extracts: hybrid lines having many cells with a normal X chromosome had high levels of HGPRT activity, but lines with few cells bearing an X chromosome had low levels. Hybrid cells bearing an X chromosome donated by bone marrow cells accumulated large amounts of polyribosomal globin messenger RNA (mRNA), suggesting that the effects of the X chromosome lie at the level of heme biosynthesis. Growth of the X-chromosome-bearing hybrid cells in dimethyl sulfoxide (DMSO)-containing medium supplemented with 10^{-4} M hemin or 10^{-3} M δ -aminolevulinic acid (ALA) gave results that indicate that the X-linked locus of bone marrow cells inhibits heme biosynthesis at the step catalyzed by ALA synthetase. In five noninducible variants examined, heme accumulation was not detected and DMSO did not stimulate an increase in the number of transferrin receptors. Three of these variants had increased chromosome numbers compared with the parental cell line, which might indicate that the altered phenotype of these cell lines is due to a change in the amount and/or arrangement of the genetic material. (34 refs)

79-2303 A Case of Chronic Myelogenous Leukemia Associated with Gastric Cancer. (Jpn) Fujii, H. (Third Dept. Internal Medicine, Kyoto First Red Cross Hosp., Kyoto, Japan). *Jpn J Clin Hematol* 19(12): 1677-1683; 1978.

The occurrence of chronic myelogenous leukemia (CML) associated with gastric cancer in a 46-yr-old Japanese woman is reported. She was admitted with complaints of hematemesis and melena. An ulcerated lesion of the gastric antrum was found through an upper gastrointestinal series and endoscopy; biopsy indicated the presence of a Group V lesion. Peripheral blood tests revealed anemia, leukocytosis with immature granulocytes, and normal neutrophil alkaline phosphatase activity. The vitamin B12 level was high. The bone marrow was markedly hypercellular, and chromosome analyses of these cells showed that the patient was positive for the Philadelphia chromosome and that she had a 46,XX, t(9;22) (q⁺;q⁺) karyotype. A diagnosis of CML associated with gastric cancer was made. The resected gastrectomy specimen contained a 2-x 2-cm Borrmann Type II gastric cancer that, upon histologic examination, was shown to be

a tubular mucinous micronodular adenocarcinoma. From 1944 to 1975, the incidence of reported cases of leukemia and coexistent primary cancer in Japan was 0.56%-0.64%. Five of the total 532 cases were CML associated with gastric cancer. (23 refs)

79-2304 Five Cases of Malignant Lymphoma Associated with Early Gastric Cancer. (Eng) Takenaka, T. (Dept. Internal Medicine and Surgery, National Cancer Center Hosp., 5-1-1, Tsukiji, Chuo-ku, Tokyo 104, Japan); Sakano, T.; Kitahara, T.; Kitaoka, H.; Watanabe, S.; Hirota, T. *Jpn J Clin Oncol* 8(2): 209-217; 1978.

The occurrence of malignant lymphoma (ML) associated with early gastric cancer in five patients (2 women aged 40 and 73 yr, 3 men aged 62, 66, and 75 yr) is reported. There were two cases of diffuse large lymphoid-type ML and three cases of Hodgkin's disease. The ML was antecedent or coincidental in four patients. The early gastric cancer was a well-differentiated adenocarcinoma in three patients and a mucinous adenocarcinoma in two. Laboratory studies revealed decreases in WBC and RBC in all five patients and decreased lymphocytes in four patients between the onsets of the different malignancies. IgM was decreased in four patients and the skin response to purified protein derivative of tuberculin was negative in 3/4 patients tested. In all five cases, complaints relating to the second neoplasms were considered at first to be related to the known primary tumors. It was not clear whether the primary neoplastic disease rendered the patient more prone to development of the second tumor or whether the cancer therapy in certain settings decreased the immune response, leading to a second neoplastic change. Malignant tumors were found in relatives of three patients. It is necessary to investigate the relationship between aging and cellular immunity in patients with ML. (18 refs)

79-2305 Sarcomas in a Child and Her Father. (Eng) Parry, D. M. (Clinical Epidemiology Branch, NCI, A521 Landow Bldg, Bethesda, MD, 20014); Mulvihill, J. J.; Miller, R. W.; Spiegel, R. J. *Am J Dis Child* 133(2): 130-132; 1979.

The occurrence of sarcomas in a 4.5-yr-old girl and her 30-yr-old father is reported. The girl had an embryonal rhabdomyosarcoma of the right foot and popliteal space, poor hearing (possibly related to recurrent ear infections), and at least four cafe au lait spots (CALs) on her trunk. CALs were not reported on any other family member. The father had an osteosarcoma at an atypical site for this tumor, the mid-humerus. He had been employed for 8 yr in a zinc smelter and had a lifelong history of residence in an area of industrial pollution. The area also had excessively high death rates in white men from bone and connective tissue cancer. The only other case of cancer in the family was an unspecified malig-

nant neoplasm in a maternal first cousin of the father. The differential etiologic diagnoses were: osteosarcoma, possibly related to occupational exposures, in the father; sporadic multiple neurofibromatosis (NF) in the daughter; hereditary NF; and familial sarcoma-carcinoma syndrome. These diagnoses are discussed and recommendations are made for family studies to determine the appropriate diagnosis. (12 refs)

- 79-2306 Angioimmunoblastic Lymphadenopathy and Immunoblastic Sarcoma. Ultrastructural Study of a Case.** (Spa) Forteza Vila, J. (Servicio Anatomia Patologica, Ciudad Sanitaria 'Juan Canalejo', La Coruna, Spain); Rodriguez Fernandez, J. M.; Villamayor Alvarez, M.; Guitian Barreiro, D. *Sangre (Barc)* 24(1): 59-72; 1979.

Chronic lymphoid leukemia was diagnosed in a 47-yr-old man hospitalized with marked asthenia and anorexia. Bone marrow and lymph node biopsies performed immediately after admission revealed angioimmunoblastic lymphadenopathy (AIL). Bone marrow, lymph node, and liver biopsies performed 6 mo later demonstrated infiltrations of immunoblastic sarcoma (IS). Histological and ultrastructural examination of the first lymph node biopsy specimen showed partial destruction of the lymph node structure with diffuse infiltration by pleomorphic lymphocytes (predominantly immunoblasts) and vascular proliferation. Examination of the second specimen showed disappearance of the vascular proliferation, total obliteration of the lymph node structure by pleomorphic lymphocytes (predominantly immunoblasts), and numerous isolated epithelioid cells. Bone marrow biopsy 6 mo later showed lymphocyte infiltration with an immunoblast predominance and destruction of the normal architecture. The marked selective erythroblastopenia and the absence of diffuse bone marrow infiltration may be explained by the existence of antierythroblast antibodies. (25 refs)

- 79-2307 Inappropriate Antidiuretic Hormone Complicating Histiocytic Lymphoma.** (Eng) Kelton, J. G. (Room 4N48, Dept. Pathology, McMaster Univ. Medical Centre, 2100 Main St. W., Hamilton, Ontario, Canada L8S 4J9); Logue, G. *Arch Intern Med* 139(3): 307-308; 1979.

The case reports of two patients with histiocytic lymphomas complicated by hyponatremia resulting from the inappropriate antidiuretic hormone (IADH) syndrome are presented. In both patients, hyponatremia appeared simultaneously with hypertonicity of the urine in the absence of signs of hypovolemia or abnormal renal or adrenal function. Hyponatremia occurred when there was max tumor bulk and not following tumor regression with therapy. (19 refs)

- 79-2308 Kaposi's Sarcoma: A Brief Review of a Rare Disease.** (Ger) Obrist, R. (Department fur In-

nere Medizin, Abteilung fur Onkologie, Kantonsspital, CH-4056 Basel, Switzerland); Hartmann, D.; Obrecht, J. P. *Onkologie* 1(1): 20-22; 1978.

A case of Kaposi's sarcoma (KS) in a 50-yr-old Bantu from Tanzania is described briefly, and the relevant literature is reviewed. Malignant degeneration of epithelial cells is most often suggested as the cytogenetic basis of KS, although reticuloendothelial and Schwann cells and pericytes have also been implicated. The frequency of KS increases linearly with age, unlike carcinomas that increase exponentially. The incidence in men is 10 times that in women. A virus etiology is suggested by the high incidence of KS in the malaria belt (Central and East Africa). The incidence of increased cytomegalovirus antibody titers is significantly higher in KS patients. Of interest is the fact that with progression of KS these titers become lower and less frequent. Disturbances of the immune system are suggested by the frequency of second tumors in KS patients. In a group of 63 patients, 18 died of a second tumor; 8/18 had malignant lymphoma. Second tumors are more common among Europeans and Americans than among African blacks; more cytostatic treatment may be the cause of this difference. (16 refs)

- 79-2309 Anaplastic Carcinoma of the Thyroid Gland. An Ultrastructural Study on Four Cases.** (Eng) Hayashi, Y. (Dept. Pathology, Hiroshima Univ. Sch. Medicine, 1-2-3 Kasumi, Hiroshima, Japan); Tokuoka, S. *Acta Pathol Jpn* 29(1): 119-133; 1979.

The ultrastructural features of four cases of anaplastic carcinoma of the thyroid, one small cell carcinoma and three giant cell carcinomas, are presented. In the small cell carcinoma, fine cytoplasmic interdigitations and junctional complexes between apposing cytoplasmic membranes of neighboring tumor cells and a few microlumina within tumor cell clusters surrounded by well-defined basal lamina were seen. In the giant cell carcinomas, occasional cytoplasmic interdigitations as well as desmosomal structures were detected even in tumor cells that were markedly pleomorphic and anaplastic. Abundant cytoplasmic organelles, including well-developed Golgi apparatus, rough endoplasmic reticulum, and a few mitochondria, were seen in the tumor cell cytoplasm of all four carcinomas. All the giant cell carcinomas showed evidence of a fairly well-differentiated tumor within the anaplastic carcinoma, indicating the probable preexistence of a more differentiated benign or malignant epithelial neoplasm that subsequently underwent anaplastic transformation. The findings support the hypothesis that these anaplastic tumors are derived from the follicular epithelium of the thyroid gland. In addition, the small cell carcinoma cells provide evidence suggesting that the functional differentiation of carcinoma cells occurs to a certain extent, but not to the extent that they are able to produce thyroglobulin. (20 refs)

- 79-2310 Seeding of Parotid Carcinoma along Vim-Silverman Needle Tract.** (Eng) Yamaguchi, K. T. (Dept. Otolaryngology, Veterans Admin. Hosp., 150 S. Huntington Ave., Boston, MA, 02130); Strong, M. S.; Shapshay, S. M.; Soto, E. *J Otolaryngol* 8(1): 49-52; 1979.

A case of parotid tumor seeding to the skin, secondary to Vim-Silverman (V-S) needle biopsy, occurred in an 82-yr-old man. During an 11-mo follow-up period after the biopsy, a slowly enlarging mass involving the skin at the biopsy site was detected. The entire tumor mass was excised. The patient died approximately 3 mo postoperatively; an autopsy could not be obtained. Histological sectioning of the surgical specimen revealed carcinoma growing in a tractlike configuration extending from the sc tumor mass to the ulcerated skin surface. The tumor was diagnosed as a poorly differentiated mucoepidermoid carcinoma of the parotid gland. This case demonstrates the possible but rare complication of V-S needle biopsy. (9 refs)

- 79-2311 Development of a Neonatal and Metastatic Murine Neuroblastoma Model.** (Eng) Sheffler, B. A. (Dept. Biological Chemistry, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033); Repman, M. A.; Schengrund, C. L. *Cancer Res* 39(3): 711-713; 1979.

A neonatal murine neuroblastoma (NB) model and a murine NB model for metastatic involvement were developed with the use of syngeneic A/Jax mice [neonates (24- to 48-hr-old mice), pups (10-day-old mice), and adults (6- to 8-wk old mice)]. The S20Y NB cell line used was cloned from the A/Jax murine C1300 NB. Dose-response studies of adult male and female mice given sc injections showed no meaningful sex-related differences in either the appearance or the growth rate of the tumors. No significant difference in tumor appearance or growth rate was observed between pups and adults. However, neonates inoculated with the same number of cells as the adults demonstrated a marked delay in tumor appearance. Neonates challenged with 5×10^5 cells showed a 75% reduction in tumor appearance compared with their adult counterparts. An inoculum of 2×10^5 S20Y cells resulted in 100% of the adult mice developing tumors within 26 days, but none of the neonates had developed tumors > 90 days postinjection. Comparison of the sc and intradermal routes of injection of NB cells was made using adult male mice. Tumors developed at approx the same rate. The intradermal tumors were removed at various stages of growth. Over 90% of the mice that underwent surgery and a similar percentage of the mice with intradermal tumors that did not have surgery subsequently developed metastases to the lymph nodes, liver, lungs, adrenals, heart, kidney, spleen, and abdominal area, sites that commonly harbor metastatic lesions in human NB. Metastases at these sites were not observed with sc inoculations. (13 refs)

- 79-2312 Development of a Metastatic Brain Tumor Model in Mice.** (Eng) Conley, F. K. (Div. Neurosurgery, Dept. Surgery, Stanford Univ. Sch. Medicine, Stanford, CA, 94305). *Cancer Res* 39(3): 1001-1007; 1979.

This study reports an easily accomplished and reliable model of metastatic tumor in the brains of female C3H/Bi mice. Five experimental groups of mice received left intracardiac injections of a syngeneic KHT sarcoma cell suspension (1×10^5 cells) and were followed until death. Two groups of mice also received 3,000 rads of radiation to a limited cardiac port 24 hr after tumor injections. All mice were completely autopsied, and the brains were examined both grossly and microscopically. Metastatic brain tumors developed in 60% to 70% of the mice; the tumor foci were parenchymal, usually multifocal, and they had wide distribution throughout the cerebrum, brainstem, and cerebellum. There was an occasional meningeal tumor, but tumors never involved the skull, choroid plexus, pituitary gland, or local extracranial structures. Cardiac irradiation did not increase the number or the mean survival of mice with metastatic brain tumors, but it did decrease the total tumor burden of individual animals by markedly reducing the incidence of metastatic lung tumors and totally preventing tumor infiltration of the heart. This demonstration of consistently produced blood-borne metastatic brain tumors in mice should provide a valuable research model that will allow the CNS to be studied for internal mechanisms and/or external factors that influence that arrest and growth of embolic tumor cells in the brain. (44 refs)

- 79-2313 Angiographic Demonstration of Infratentorial Tumors with Concordant Manifestation, Localization, and Histology in Monozygotic Twins.** (Ger) Voigt, K. (Medizinisches Strahleninstitut, Abteilung für Neuroradiologie, Röntgenweg 11, 7400 Tübingen, W. Germany); Marquardt, B. *ROEFO* 130(1): 89-94; 1979.

The occurrence of craniospinal subependymomas with identical manifestations, localization, and histology in a pair of monozygotic twins is reported. Literature cases of histologically confirmed concordant brain tumors in seven sets of twins and three other cases suspected to be concordant are reviewed. The twins reported here were healthy until age 22. The localization of the tumors was established by computer tomography (CT), angiography, ventriculography, and surgery, and it was found to be nearly identical. The tumors had grown through the foramen magnum, and they extended from the fourth ventricle to the second cervical vertebra. The tumors showed no signs of malignancy, and there have been no indications of regrowth during the 3 postoperative yr. A CT scan was used for follow-up. Genetic factors or a hereditary disposition may play a role in the development of cerebral tumors in twins. (24 refs)

- 79-2314 Retinoblastoma with 13q--Chromosomal Deletion Associated with Maternal Paracentric Inversion of 13q.** (Eng) Sparkes, R. S. (Div. Medical Genetics, Dept. Medicine, Center Health Sciences, Univ. California, Los Angeles, CA, 90024); Muller, H.; Klisak, I.; Abram, J. A. *Science* 203(4384): 1027-1029; 1979.

Cytogenetic studies in a girl with sporadic unilateral retinoblastoma and mental retardation demonstrated an interstitial deletion in the long arm of chromosome 13. Her mother was found to have a paracentric inversion of one chromosome 13; the deleted chromosome in the daughter was derived from the mother's normal chromosome 13. (5 refs)

- 79-2315 Complete Heart Block Caused by Metastatic Tumor of the Heart. Report of One Case.** (Fre) Almange, C. (Service de Cardiologie B, Centre Hospitalier Universitaire, 2 rue de l'Hotel-Dieu, 35011 Rennes Cedex, France); Lebreteux, T.; Louvet, M.; Courgeon, P.; Guerin, D.; Leborgne, P. *Sem Hop Paris* 50(45/46): 1419-1424; 1978.

An epidermoid carcinoma of the esophagus metastasized to the heart of a 59-yr-old man. The metastases were located in the interventricular septum and caused complete atrioventricular block. Histological examination showed destruction of the conduction fibers. The patient lived 10 mo after diagnosis, an unusually long survival for atrioventricular metastatic block. (32 refs)

- 79-2316 Metastatic Tumors in the Temporal Bone--A Pathophysiologic Study.** (Eng) Jahn, A. F. (Banting Inst., 100 College St., Room 81, Toronto, Canada); Farkashidy, J.; Berman, J. M. *J Otolaryngol* 8(1): 85-95; 1979.

Pathophysiologic studies were made of 19 temporal bones (TPB) from 11 patients (7 men and 4 women aged 18-90 yr) who had metastatic TPB disease from a distant primary tumor. Clinical features included a high incidence of occult TPB involvement (7/10 clinically documented cases), a considerable incidence of melanoma (3/10 cases), and a variable correlation between clinical findings and pathologic localization of the tumor in the TPB. Two distinct modes of tumor spread within the TPB were observed on pathologic examination: vascular-osseous (petrous apex, mastoid, middle ear, and external canal) and perineural (nerves in the internal canal branches and labyrinthine end-organs). Every case was involved by one or both of these routes, and no case of cerebrospinal fluid-borne metastasis to the perilymphatic space was seen. The earliest metastatic focus appeared to gain a foothold in the marrow-containing portion of the petrous bone. Perineural tumor spread was distinct from and unrelated to the progress of bony tumor involvement. The initial point of entry into the nerve trunk was evidently associated with intraneural vessels, although in some cases the relationship was not readily demonstrated. The external canal was

involved extensively in spite of an intact tympanic membrane. Considering that the initial focus of tumor often lies within the petrous bone, hidden by apparently uninvolved dura and petrous ridge, it may well escape detection at routine autopsy. TPB metastasis may be the initial sign of cancer or the first evidence of skull base invasion. Occult metastases may be discovered through TPB tomography. (10 refs)

- 79-2317 Nasopharyngeal Carcinoma in Siblings.** (Eng) Fischer, R. A. (Yale-New Haven Hosp., New Haven, CT); Wharam, M. D.; Kashima, H. K. *Ear Nose Throat J* 58(2): 93-97; 1979.

The third documented occurrence of a familial aggregation of nasopharyngeal carcinoma (NPC) in the US is presented, and the literature on all familial aggregations of this tumor is reviewed. NPC was diagnosed in a 13-yr-old boy whose initial symptoms were swelling of the right parotid area and several spontaneous nosebleeds. Seven years later, NPC was diagnosed in his 17-yr-old sister, whose initial symptom was a high right neck mass that gradually grew and became tender. Thirty-three familial clusters among Chinese families have been reported, with horizontal associations (sibling-sibling) being more common than vertical associations (parent-child). In a retrospective survey in Hong Kong, the risk of NPC among close family members of NPC patients (3%) was found to be 10-fold greater than that for family members of patients with other types of cancer. Among non-Orientals, 10 familial clusters of NPC have been reported. The male:female ratio among these patients is 2:1. Sixty-five percent of the patients were <30 yr old at the time of onset, and they had a younger age distribution than NPC patients in general. The ages at onset for affected sibs were similar, and the av difference in date of onset within families was <4 yr. The occurrence of this disease in families clustered closely in time is consistent with a hypotheses of a common environmental causative agent and/or a genetic predisposition. (18 refs)

- 79-2318 Changes in Bronchial Epithelium in Relation to Cigarette Smoking, 1955-1960 vs. 1970-1977.** (Eng) Auerbach, O. (151B, Veterans Admin. Medical Center, E. Orange, NJ, 07019); Hammond, E. C.; Garfinkel, L. *N Engl J Med* 300(8): 381-386; 1979.

To determine whether the drop in tar and nicotine levels in cigarette smoke that began in the 1950's has been reflected in less extensive histologic changes in the bronchial epithelium of cigarette smokers, 20,424 bronchial tube sections taken at autopsy from men not dying of lung cancer were examined. The sections were taken from 211 men who died between 1955 and 1960 (Group 1) and 234 men who died between 1970 and 1977 (Group 2). Regular smokers numbered 154 in Group 1 and 181 in Group 2. Changes studied included basal-cell hyperplasia, loss of cilia, and occurrence of cells

with atypical nuclei. In both groups, these changes occurred much less frequently in nonsmokers than in cigarette smokers, and they increased in frequency with the amount of smoking, adjusted for age. Sections with advanced histologic changes in Group 1 subjects occurred in 0% of nonsmokers, in 2.6% of those smoking 1-19 cigarettes daily, in 13.2% of those smoking 20-39 cigarettes daily, and in 22.5% of those smoking > 40 cigarettes daily. In Group 2, the percentages were 0%, 0.1%, 0.8%, and 2.2%, respectively. These results are consistent with evidence from epidemiologic studies indicating that death rates from lung cancer are lower among men who smoke low-tar/nicotine cigarettes than among men who smoke the same number of high-tar/nicotine cigarettes per day and with the fact that there has been a great decrease in the tar/nicotine content of cigarette smoke over the last 25 yr. (12 refs)

79-2319 Thrombocytosis and Primary Bronchial Carcinoma. Study of 164 Patients with Bronchial Carcinoma. (Fre) Bouvenot, G. (Service de Medecine Interne, Hotel-Dieu, 6 place Davel, 13224 Marseille Cedex 1, France); Bartolin, R.; Dugue, P.; Heim, M.; Delboy, C.; Charpin, J. *Sem Hop Paris* 55(1/2): 26-29; 1979.

In a series of 164 patients with primary bronchial carcinoma (114 malpighian epidermoid, 17 anaplastic small cell, and 33 adenocarcinoma), 60 had thrombocytosis (platelet count > 400,000/mm³). No statistical relationship was observed between elevated platelet count and the histological type of tumor, presence of the inflammatory syndrome (serum α -globulin > 11%, blood fibrin > 4.4 g/liter, sedimentation rate > 40), or presence of metastases. A significant correlation was observed between thrombocytosis and anemia (Hb < 12 g/100 ml). Respiratory function studies did not show any correlation with thrombocytosis. A platelet count when correlated with x-ray studies may be of value in the diagnosis of lung cancer. (13 refs)

79-2320 Lung Cancer and Pneumothorax (2 Letters to Editor). (Eng) Snell, N. J. (Central Chest Clinic, Reading, Berkshire, England); Hyde, L.; Hyde, C. I. *JAMA* 241(11): 1107; 1979.

In contrast to previous statements, undiagnosed lung cancer may be present in patients with pneumothorax (PT) who are < 40 yr of age. PT occurs more commonly with secondary malignant lung disease, particularly metastases from bone sarcomas, and this is nearly always seen in those younger than 40 yr. At least 68 cases of PT with primary lung cancer and 86 cases with metastatic disease have been reported. However, a previously recorded case and the comments on it was intended to refer only to patients with simultaneous primary lung cancer and spontaneous PT. (5 refs)

79-2321 Malignant Transformation of Cicatricial Stenosis (due to a Caustic Agent) of the Esophagus. (Fre) Gaillard, J. (Service O.R.L., Hopital de la Croix-Rousse, 93 Grande-Rue-de-la-Croix-Rousse, 69004 Lyon, France); Haguenaer, J. P.; Romanet, P. *Ann Otolaryngol Chir Cervicofac* 95(6): 395-399; 1978.

Four patients in whom esophageal carcinoma developed at healed chemical burn sites are described. The carcinomas were observed between 29 and 57 yr following the initial injury. Trauma due to artificial dilatation of the stenosed esophagus may also be involved in the development of the carcinoma. (no refs)

79-2322 Distant Metastases to Bone from Bladder Carcinoma: Report of Three Cases. (Eng) Dunnick, N. R. (Dept. Diagnostic Radiology, NIH, Clinical Center, Building 10, Room 6S211, Bethesda, MD, 20014); Anderson, T. *Am J Roentgenol* 132(3): 469-470; 1979.

The cases of three patients with distant bone metastases from transitional cell carcinoma of the bladder are presented. The sites of metastases in the first two patients, the right talus and the right mandible, respectively, are rare; deep vein thrombosis and dental abscess were initially suspected in each case. In the third patient, metastases occurred in the right pedicle of T6 and in the parietal region of the skull. (6 refs)

79-2323 Primary Malignant Tumor of the Liver Associated with the Ingestion of Oral Contraceptives. (Fre) Leclerc, J. (Clinique Medicale et Endocrinologique, CHU de Nancy, Hopital de Brabois, F 54500 Vandoeuvre-Nancy, France); Meot, B.; Marchal, F.; Mizrahi, R.; Collard, F.; Begue, J. Y.; Rauber, G.; Hartemann, P. *Nouv Presse Med* 8(5): 346-349; 1979.

A case of primary liver carcinoma occurring in a 42-yr-old woman who had been taking oral contraceptives for 10 yr is presented. The diagnosis was made by biopsy. Twenty-one similar cases have been reported in the literature. There are also approx 200 literature cases of benign liver tumor in patients that had been taking oral contraceptives, but the etiological role of oral contraceptives in either benign or malignant tumors has not been established. The regression of certain benign tumors when the steroids are discontinued is the essential argument in favor of this association. In some patients, the association of benign lesions with hepatic carcinoma suggests a single pathogenesis. (23 refs)

79-2324 Hepatocellular Carcinoma in Siblings. (Ger) Sitzmann, F. C. (Universitäts-Kinderkliniken Erlangen, 6650 Homburg/Saar, W. Germany); Lindinger, A. *Therapiewoche* 29(8): 1287-1291; 1979.

The cases of a brother and sister who died in childhood of hepatocellular carcinoma (HCC) are reported, along with the incidence of liver disease in their family. The boy had icterus at 2 wk and at 3 mo of age. He was exposed at 4 mo to an aunt who, 4-5 mo previously, had hepatitis, and at 7 mo he developed marked icterus. A biopsy at 10 mo showed periportal fibrosis of the liver. Cortisone was given several times. The liver rapidly increased in size starting at age 6.5, and HCC was diagnosed soon thereafter. The boy died at age 7. An extensive, multicentric liver carcinoma that had invaded the portal vein but showed no signs of metastasis was found at autopsy. The sister was first examined for an enlarged abdomen at 1.5 yr of age; liver cirrhosis was found at laparoscopy. The disease began to progress rapidly, with sizable enlargement of the liver, when she was 5.75 yr old. At autopsy finely granular cirrhosis, a multicentric HCC that had extended into the portal vein and both of its branches, and lung metastases were found. The disease courses of the siblings seemed very similar. Their paternal grandfather had γ -chain plasmacytoma. Both maternal grandparents had liver cirrhosis that developed between age 30-40. The maternal grandfather, in whom the disease was not progressing, was positive for anti-hepatitis B surface antigen (HBsAg) and anti-HB core antigen and negative for HBsAg. The children's mother had chronic aggressive hepatitis at age 28 and was positive for HBsAg. A 9-yr-old sibling, who was examined carefully, appears to be healthy. (38 refs)

- 79-2325 **Electrophoretic Variant of Fetal Intestinal Alkaline Phosphatase in a Patient with Cirrhotic Liver.** (Eng) Kudo, S. (Third Dept. Internal Medicine, Osaka Univ. Sch. Medicine, Fukushima 1-1-50, Fukushima-ku, Osaka 553, Japan); Higashino, K.; Yamamura, Y. *Gann* 70(1): 15-19; 1979.

Two enzymes observed in the hepatic tissue of a patient with posthepatic cirrhosis were studied. On thin-layer polyacrylamide gel electrophoresis, the alkaline phosphatase (AP) isoenzyme of a liver extract from this patient showed a broad band with high activity and two additional bands with lower activity at the anodal side. These two anodal bands and the Kasahara isoenzyme (a fetal intestinal AP found in the sera of hepatoma patients) were slightly inhibited by L-homoarginine and almost completely inhibited by L-phenylalanine. Like the fetal intestinal AP, the anodal bands were moderately stable to heat treatment and were not inactivated by treatment with neuraminidase (1 mg/ml) or sodium dodecyl sulfate (10 g/liter). The two enzymes cross-reacted with anti-adult intestinal AP antibody, but not with antibody specific for placental AP. The enzymes therefore seem to be variants of a fetal intestinal AP. Their occurrence in cirrhotic liver along with their reported occurrence in hepatoma support the concept that cirrhosis of the liver is a precancerous state. (13 refs)

- 79-2326 **Paraneoplastic Syndromes of the Kidney.** (Fre) Jimenez Cruz, J. F. (Service d'Urologie, Cite Sanitaire de la Securite sociale, Barcelona, Spain); Rioja Sanz, C.; Garcia-Lopez, F.; Sole-Balcells, F. *Sem Hop Paris* 55(1/2): 74-79; 1979.

Paraneoplastic clinical signs observed in 10 patients (4 men, 6 women, aged 44-72 yr) with carcinoma of the kidney are reported. Hepatic dysfunction was the most common (41.5%) sign, followed by pain (38%), palpable mass (35%), and fever (18.8%). (31 refs)

- 79-2327 **Adenomatous Hyperplasia of the Gallbladder in Chronic Cholecystitis and Its Significance in Carcinogenesis.** (Pol) Piegza, S. (Oddz. Chirurgii Ogolnej, ZOZ dla Gornikow, ul. Sokolowskiego 4, 58-309 Walbrzych, Poland); Tyszkiewicz, S.; Turczynski, J.; Szklarz, Z. *Wiad Lek* 31(23): 1667-1670; 1978.

Adenomatous hyperplasia of the gallbladder was found in 94/227 patients who underwent surgery for chronic cholecystitis. Investigation of the surgical specimens revealed chronic glandular cholecystitis in 77.6% of the 94 patients (av age 44.9 yr), chronic adenomatous cholecystitis in 15.9% (av age 48.8 yr), and columnar cell adenocarcinoma in 6.3% (av age 45.5 yr). In agreement with data in the literature, these findings indicate that gradual adenomatous changes lead to gallbladder carcinoma. (12 refs)

- 79-2328 **Significance of Blood Vessel Invasion in the Involved Lymph Node as a Predictor of Blood-borne Metastases in Breast Cancer--Further Report.** (Eng) Izuo, M. (Dept. Surgery, Gunma Univ. Sch. Medicine, 3-39-15, Showa-machi, Maebashi-shi, Gunma 371, Japan); Akabani, O.; Okano, A.; Kawai, T. *Jpn J Clin Oncol* 8(2): 101-104; 1978.

Two hundred and fifty-six patients who had undergone radical mastectomy were investigated for blood vessel invasion in the primary tumor (BVIT), and 106 of these patients with regional lymph node metastasis were examined for blood vessel invasion within and in the vicinity of the involved lymph node (BVIN). BVIT was found in 69 (27.0%) patients. These patients, particularly those with regional node metastases (19.9% of the total population), showed a higher incidence of blood-borne distant metastases than those without BVIT. The incidence of blood-borne metastases was 6.1% in patients with neither BVIT nor BVIN, 12.5% in patients with BVIT but not BVIN, 40.9% in those with BVIN but not BVIT, and 48.6% in those with BVIT and BVIN. When the patients with positive BVIN were divided into three subgroups according to the grade of invasion, the incidence of blood-borne distant metastases was found to increase according to the grade of BVIN. The data suggest that blood vessel invasion, especially of the involved lymph nodes, is an important predictor of postoperative distant metastases. (9 refs)

79-2329 Malignant and Benign Papillary Lesions of the Breast. (Eng) Murad, T. M. (Div. Surgical Pathology and Cytology, Univ. Alabama Medical Center, University Station, Birmingham, AL, 35294); Swaid, S.; Pritchett, P. *Hum Pathol* 8(1): 379-390; 1977.

Criteria that may be helpful in classifying various proliferative changes of the breast and in separating papillary carcinoma from other benign papillary lesions are presented. Epithelial and papillary proliferations of the breast include papillomatosis, terminal duct hyperplasia, atypical duct hyperplasia, intraductal papilloma, and multiple papillomas. Papillary carcinoma of the breast tends to involve more than one duct system and is frequently seen after biopsy of a gross lesion rather than as an incidental microscopic finding. Papillary carcinoma tends to form one of four basic microscopic patterns, and frequently there is a mixture of two or more patterns within the same tumor. These patterns comprise the papilliform, reticular, cribriform, and microcystic types. The true incidence of benign proliferative changes in fibrocystic disease and the significance of these lesions in the later development of cancer were determined by studying 200 randomly selected cases of fibrocystic disease seen at least 10 yr earlier. Forty patients had intraductal papillomatosis or epithelial cell hyperplasia. The average age of these 40 patients was 44.5 yr (range 24-65). In 20 patients, the papillomatosis coexisted with the epithelial cell hyperplasia. None of the patients for whom complete follow-up data are available (up to 14 yr) developed cancer. Ultrastructural and histochemical studies suggest that both epithelial and myoepithelial cells participate in papillary breast lesions. (19 refs)

79-2330 Sexual Precocity and Thoracic Polyembryoma: Klinefelter Syndrome (Letter to Editor)? (Eng) Floret, D. (Clinique Medicale Infantile B, Hopital Edouard-Herriot, Place d'Arsonval, 69374 Lyon Cedex 2, France); Renaud, H.; Monnet, P. *J Pediatr* 94(1): 163; 1979.

The case of an 8-yr-old boy with Klinefelter's syndrome and sexual precocity due to a thoracic human chorionic gonadotropin (HCG)-producing teratoma is presented. The Klinefelter's syndrome was suspected because of a relative impairment of testicular enlargement in relation to plasma testosterone levels (0.35 $\mu\text{g}/\text{deciliter}$). This diagnosis was confirmed by the presence of testicular sclerohyalinization and by the karyotype (47 XXY). Plasma and tumor HCG levels were 25 milli-IU (mIU)/ml and 2,500 mIU/g, respectively. (2 refs)

See also:

*(Rev.): 79-1803, 79-1807, 79-1814, 79-1823, 79-1835, 79-1857, 79-1858, 79-1860, 79-1861, 79-1862, 79-1863, 79-1866, 79-1867, 79-1868, 79-1869, 79-1870, 79-1871, 79-1872, 79-1874, 79-1876, 79-1877, 79-1878, 79-1881, 79-1882, 79-1889, 79-1890, 79-1891, 79-1892, 79-1893, 79-1894, 79-1895.

*(Chem.): 79-1906, 79-1914, 79-1920, 79-1922, 79-1932, 79-1937, 79-1950, 79-1966, 79-1967, 79-1968, 79-1972, 79-1974, 79-1975, 79-1982, 79-1989, 79-1992, 79-1999, 79-2000, 79-2005, 79-2013, 79-2017, 79-2020, 79-2026, 79-2035, 79-2037, 79-2049, 79-2081, 79-2090, 79-2091, 79-2093, 79-2094, 79-2095, 79-2097, 79-2100, 79-2101.

*(Phys.): 79-2106, 79-2111, 79-2112, 79-2114, 79-2115, 79-2117, 79-2119, 79-2120.

*(Viral): 79-2150, 79-2166, 79-2180, 79-2203, 79-2204, 79-2215, 79-2232, 79-2234.

*(Immun.): 79-2287.

*(Epid.-Biom.): 79-2347, 79-2348, 79-2349, 79-2350, 79-2351, 79-2352, 79-2354, 79-2355, 79-2356, 79-2373, 79-2378.

- 79-2331 Occurrence of Non-Hodgkin's Lymphoma after Therapy for Hodgkin's Disease.** (Eng) Krikorian, J. G. (Div. Medical Oncology, Dept. Medicine, Stanford Univ. Sch. Medicine, Stanford, CA, 94305); Burke, J. S.; Rosenberg, S. A.; Kaplan, H. S. *N Engl J Med* 300(9): 452-458; 1979.

The clinical and pathologic features of six cases of non-Hodgkin's lymphoma (NHL) (diffuse undifferentiated in 4, diffuse histiocytic in 2) in patients treated with both radiation and chemotherapy for Hodgkin's disease (HD) were studied. Five of the six patients were among a study group of 579 HD patients that were prospectively followed since diagnosis. Five of the patients showed abdominal or gastrointestinal involvement with NHL. In no case was evidence of HD present when the NHL was diagnosed. In the study group, the actuarial risk of NHL at 10 yr was 4.4% and that of acute leukemia was 2.0 %. In the subgroup of patients receiving both radiation and chemotherapy, the actuarial risks of NHL and acute leukemia at 10 yr was 15.2% and 3.9%, respectively. Acute myelocytic leukemia occurred an av of 54 mo after the diagnosis of HD, whereas NHL occurred an av of 89 mo after the diagnosis. It is concluded that NHL may occur late in the course of treatment of HD and that, like acute leukemia, it may result from combined-modality therapy. (39 refs)

- 79-2332 Primary Malignant Liver Tumors: Association with Oral Contraceptives.** (Eng) Vana, J. (Dept. Epidemiology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263); Murphy, G. P. *NY State J Med* 79(3): 321-325; 1979.

Data on 149 women and 138 men with primary malignant liver tumors reported by 477 US hospitals during 1970-1975 were analyzed by sex, age, histologic diagnosis, and, in female patients, by history of oral contraceptive use. The malignant tumors were hepatocellular carcinoma (HCC: 84.6% and 80.4% in women and men, respectively), cholangiocarcinoma (8.7% and 14.5%), or combined HCC and cholangiocarcinoma (6.7% and 5.1%). Two male patients had a strong family history of liver tumors. Long-term use of alcohol was noted in eight male HCC patients, and two male patients had been under long-term treatment for ulcerative colitis. One male HCC patient (24 yr old) had been treated with androgen injections for infertility and another (29 yr old) had a history of uncorrected, undescended testis. Of the 126 HCC in women (15-45 yr old), a history of oral contraceptive use was found in 31% of patients; in the age group

26-35 yr, it was 43%. Significant ip hemorrhage occurred in 17% of the HCC in oral contraceptive users. The results of this survey neither confirm nor disprove an association between oral contraceptive use and malignant liver tumors. However, literature findings, ie, differences in the frequency of malignant tumors among users and nonusers of oral contraceptives in the reproductive age groups and certain similarities between benign and malignant liver tumors in users, warrant systematic review and follow-up of other large series of liver tumors. (36 refs)

- 79-2333 Effects of Long-Term Estrogen Replacement Therapy. II. Neoplasia.** (Eng) Hammond, C. B. (Duke Univ. Medical Center, P.O. Box 3143, Durham, NC, 27710); Jelovsek, F. R.; Lee, K. L.; Creasman, W. T.; Parker, R. T. *Am J Obstet Gynecol* 133(5): 537-547; 1979.

The effects of long-term estrogen therapy on the incidence of neoplasia were analyzed retrospectively in two groups of hypoestrogenic women that had been observed by a single group of physicians for at least 5 yr. One group (301 patients) had received replacement estrogen therapy for > 5 yr, and the other (309 patients) had received no estrogen treatment. In each group, 207 women had uteri in situ. Incidence figures for neoplasia (gynecologic, breast, and all sites) were compared between the two groups and with the Third National Cancer Survey, yielding a risk ratio for the development of adenocarcinoma of the endometrium among estrogen-treated women of 3.8 and 9.3, respectively. There was no increase among any other malignancies. The addition of synthetic progestin to the estrogen therapy provided significant protection against the likelihood of developing endometrial cancer and did not reduce previously reported metabolic benefits of estrogen treatment. Data pertaining to estrogen use and details of the patients with endometrial carcinoma (11 in the estrogen-treated group, 4 in the untreated group) are presented. (20 refs)

- 79-2334 A Case Control Study of Gastrointestinal and Urinary Tract Cancer Mortality and Drinking Water Chlorination.** (Eng) Alavanja, M. (Sch. Health Sciences, Hunter Coll., New York, NY, 10029); Goldstein, I.; Susser, M. *Water Chlorination* 2: 395-409; 1978.

To assess the potential cancer hazard associated with drinking chlorinated water, a case-control study was made of 3,446

people who died from gastrointestinal (GI) or urinary tract (UT) cancer in seven New York counties between 1968 and 1970 and 3,444 individually matched controls. There was a statistically significant excess of GI and UT cancer deaths among women living in urban areas of Erie County and among men living in urban areas of Erie and Rensselaer counties. Similar, but nonsignificant, trends were demonstrated for Schenectady and Allegany counties. GI and UT cancer deaths were significantly elevated among men and women in the chlorinated water areas of Erie and Schenectady counties and among men in the chlorinated water areas of Rensselaer county. Residents of Cattaraugus, Chautauqua, and St. Lawrence counties showed no excess GI or UT cancer mortality associated with living in urban or chlorinated water areas. Urban, but not rural, chlorinated water areas showed significantly increased mortality from lung cancer compared with nonchlorinated water areas. No correlation between GI and UT cancer mortality and inorganic ion concentrations was demonstrated. Voluntary reduction of the chloroform concentrations in potable water to $< 100 \mu\text{g/liter}$ is highly desirable. (7 refs)

79-2335 Epidemic Problems and Chlorination of Drinking Water and Sewage in the Federal Republic of Germany. (Eng) Muller, G. (Inst. Water, Soil and Air Hygiene, Federal Health Office, Berlin, W. Germany). *Water Chlorination* 2: 483-492; 1978.

Within the last 40 yr, there has been an approx 60% increase in all cancer-related deaths in West Germany. However, gastrointestinal and stomach cancers, the main types that might be induced by drinking water containing chlorinated organic compounds, have decreased. Statistics for regions using unchlorinated and slightly chlorinated drinking water showed the same trend as that found for the entire country. Thus, there is no evidence that chlorination of drinking water promotes cancer. (8 refs)

79-2336 A Study on the Aetiological Factors of Bilharzial Bladder Cancer in Egypt--1. Nitrosamines and Their Precursors in Urine. (Eng) El-Merzabani, M. M. (Dept. Cancer Biology, Cancer Inst., Cairo Univ., Cairo, Egypt); El-Aaser, A. A.; Zakhary, N. I. *Eur J Cancer* 15(3): 287-291; 1979.

The levels of nitrosamines (NA's) and their precursors in the urine of normal Egyptians and Egyptians with bilharzial infestations, bladder cancer, and other types of cancer were investigated. The urinary pH's were similar in all groups, whereas the thiocyanate levels were higher in the patients with bilharzial infestation and bladder cancer (34 and 39 ppm, respectively) than in those with no cancer or nonbladder cancer (21 and 24 ppm, respectively). Nitrate, which was present in the urine of 3/10 patients with bilharzial infestation and 7/15 patients with bladder cancer, was not present in the urine of

normal subjects and was present in the urine of only 1/14 subjects with nonbladder cancer. Endogenous NA's were present in urine samples from 2 normal subjects, 3 patients with bilharzial infestation, 15 patients with bladder cancer, and 6 patients with nonbladder cancer. After chemical nitrosation of the urine at pH 4, total NA's were $2,103$ and $2,314 \times 10^{-9}$ g/liter in the bilharzial and bladder cancer patients, respectively, compared with only 63.2 and 393×10^{-9} g/liter in the normal subjects and those with nonbladder cancer, respectively. Only in the urines from the bladder cancer patients could NA's be formed at pH 7. (11 refs)

79-2337 Comparison of Biochemical and Questionnaire Estimates of Tobacco Exposure. (Eng) Vogt, T. M. (Health Services Res. Center, Kaiser Foundation Hosps., 4610 S. E. Belmont St., Portland, OR, 97215); Selvin, S.; Hulley, S. B. *Prev Med* 8(1): 23-33; 1979.

The magnitude and independence of the association of 17 variables from a smoking questionnaire with levels of expired air CO and of serum thiocyanate (SCN) were determined by multiple regression analysis. The test cohort comprised 142 men (aged 35-57) enrolled in a multicenter coronary heart disease prevention study. The reported number of cigarettes smoked per day was the strongest questionnaire variable, and it accounted for 24% of the variation in the SCN + CO index. Only two other variables added significant information to the multiple regression--the time elapsed since last smoking (6%) and the longest time the smoker had ever quit (6%). The remaining 14 questionnaire variables together added 13% to the multiple regression of the SCN + CO index. The chief conclusion, which was confirmed by covariance analysis, is that questionnaire measures of dosage such as reported depth of inhalation, the amount of each cigarette smoked, and the use of filters may contain only trivial information on habitual tobacco exposure beyond that already available from reported smoking frequency. The CO and SCN analyses provide an objective and practical addition to estimates of tobacco exposure from questionnaire responses. (29 refs)

79-2338 A Study on the Aetiological Factors of Bilharzial Bladder Cancer in Egypt--2. Nitrosamines and their Precursors in Egyptian Dairy Products. (Eng) El-Aaser, A. A. (Dept. Cancer Biology, Cancer Inst., Cairo Univ., Cairo, Egypt); El-Merzabani, M. M.; Zakhary, N. I. *Eur J Cancer* 15(3): 293-298; 1979.

Milk, yoghurt, and four types of cheese consumed by Egyptians were analyzed for the presence of nitrosamines (NA's). NA's were not detected in blue cheese or yoghurt, and they were detected at low levels (3.2 and 9.7×10^{-9} in two milk samples. Contamination ranging from 20 to 160×10^{-9} g was found in 3/10 samples of cottage cheese, 7/10 samples of white cheese, and 6/9 samples of salted cheese. Only volatile NA's were detected in two samples of white cheese and three

of salted cheese ($20-40 \times 10^{-9}$ g). The optimum pH for the nitrosation of amines present in white and cottage cheese was 1 and 4, respectively and that for the blue and salted cheeses was 3. Chemical nitrosation yielded large amounts of extractable NA's in the samples. The highest levels were found in blue cheese, with $> 60\%$ of the NA's being volatile. The lowest levels were found in cottage cheese, with $> 50\%$ being volatile. Milk and yoghurt contained much lower concentrations of NA's, and most were not volatile. The daily consumption of salted cheese and drinking water with a high nitrate content, along with a heavily infected urinary bladder due to bilharzial infestation, might contribute to the high incidence of bladder cancer among Egyptian farmers. (19 refs)

- 79-2339 Statistical Analysis of Epidemiological Data from a Chromium Chemical Manufacturing Plant.** (Eng) Hill, W. J. (Buffalo Res. Lab., Allied Chemical Corp., 20 Peabody St., Buffalo, NY, 14210); Ferguson, W. S. *J Occup Med* 21(2): 103-106; 1979.

Probability window analysis was applied to the incidence of bronchogenic carcinoma in a group of chromium chemical manufacturing workers over the period 1929-1977. A significant downward trend in reported bronchogenic carcinoma was found that coincided with major process improvements made in 1951 (new bichromate plant) and 1961 (new chromic acid plant). Also, there have been no reported cases of bronchogenic carcinoma among persons who started their employment after 1957, even though one or more cases might have been expected from the local incidence in this age group. Because of the correlation over time between reduced incidence of bronchogenic carcinoma and lower chromium exposure levels, the improved working environment has to be considered a major contributing factor to the favorable trend. (7 refs)

- 79-2340 Mortality Study of Bleachers and Dyers.** (Eng) Newhouse, M. L. (TUC Centenary Inst. Occupational Health, England). *Ann Occup Hyg* 21(3): 293-296; 1978.

The causes of death among 1,429 men employed in the dyeing industry in Yorkshire, England, prior to 1936 and dying between 1957 and 1968 were studied. The results were compared with data from the general population at the relevant period. Approx two-thirds of the dye workers were 65 yr or older at death. There were small excesses due to cancer and respiratory diseases, but the differences between the observed and expected figures were not statistically significant. There was no indication of a particular risk in this group and no excess mortality from cancer of the bladder. (8 refs)

- 79-2341 A Dosage Response Curve for the One Rad Range: Adult Risks from Diagnostic Radiation.** (Eng) Bross, I. D. (Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263); Ball, M.; Falen, S. *Am J Public Health* 69(2): 130-136; 1979.

A new biostatistical technology to be used in the development of mathematical models for the relationship between radiation exposure and leukemia or other diseases is described. A dose-response curve for the exposure range between 100 millirads and 10 rads ("one rad range") was developed from data on men exposed to ordinary diagnostic radiation. The findings are based on approx 220 men with nonlymphatic leukemia and > 270 random-sample controls from the Tri-State Survey (New York, Maryland, and Minnesota). The new findings suggest that the estimates previously obtained by extrapolation from high-dose levels to low-dose levels underestimate the actual hazards by an order of magnitude. The new dose-response curves indicate that linear extrapolation fails because it disregards the subgroups in the general population that are particularly vulnerable to x-rays. There are immediate implications concerning the use of medical x-rays in screening or for routine purposes. The past risk-benefit calculations were based on extrapolative estimates, and they require drastic revision. Uses of x-rays that were previously marginal are now clearly contraindicated. (12 refs)

- 79-2342 Possible Induction of Basal Cell Carcinoma by External Alpha Radiation in Uranium Mine Workers.** (Cze) Sevcova, M. (Kozni oddeleni, ZUNZ Uranoveho prumyslu, Plzenska 77, 261 01 Pribram I., Czechoslovakia); Horacek, J.; Sevc, J. *Cas Lek Cesk* 117(46): 1442-1444; 1978.

The incidence of basal cell carcinoma of the skin was studied in uranium miners exposed to alpha radiation. The annual incidence of basal cell carcinoma was 7.65/10,000 in uranium miners exposed for 5-10 yr, vs an expected incidence of 0.63/10,000. For miners whose length of employment exceeded for 10 yr, the annual incidence was 13.15/10,000 vs an expected value of 0.67/10,000. The incidence was 1.08/10,000 (expected value 1.43/10,000) in uranium mine workers who were not involved in underground mining operations. The cumulated dose equivalent in the basal layer of the epidermis after long years of exposure proved to be $> 1,000$ roentgen-equivalents-man (rem). The av coefficient of risk per unit of dose equivalent was estimated to be 5×10^{-7} /rem/yr. (11 refs)

- 79-2343 Childhood Leukemias Associated with Fallout from Nuclear Testing.** (Eng) Lyon, J. L. (Dept. Family and Community Medicine, Univ. Utah Coll. Medicine, 50 N. Medical Drive, Salt Lake City, UT, 84132); Klauber, M. R.; Gardner, J. W.; Udall, K. S. *N Engl J Med* 300(8): 397-402; 1979.

Because of continuing concern over the possible carcinogenic effects of low-level radiation, the population of Utah was studied because of its exposure to fallout from 26 nuclear tests between 1951 and 1958. Certain rural counties (high-fallout counties) received most of the fallout during that period. All deaths from childhood cancers occurring in the entire state between 1944 and 1975 were reviewed and assigned to a cohort of either high or low exposure, depending on whether they were < 15 yr old between 1951 and 1958. For reasons unknown, leukemia mortality among the low-exposure cohort in the high-fallout counties was about half that of the US population and the population of the remainder of the state. Mortality increased by 2.44 times (95% confidence, 1.18 to 5.02) to just slightly above that of the US in the high-exposure cohort residing in the high-fallout counties, and it was greatest in 10- to 14-yr-old children. For other childhood cancers, no consistent pattern was found in relation to fallout exposure. The increase in leukemia deaths could be due to fallout or to some other unexplained factor. (23 refs)

79-2344 Primary Liver Cell Cancer in Britain - A Viral Aetiology? (Eng) Bassendine, M. F. (Dept. Medicine and Pathology, Royal Free Hosp., Hampstead, London NW3, England); Chadwick, R. G.; Lyssiotis, T.; Thomas, H. C.; Sherlock, S.; Cohen, B. J. *Br Med J* 1(6157): 166; 1979.

The incidence of hepatitis B virus (HBV) infection and alcoholism among 24 British Caucasians with primary liver cell cancer (PLCC) was studied. Nineteen of the patients were men, and the mean age was 55 yr. Sixteen patients were positive for HB core antibody. Six of these patients were positive for HB surface antibody. Thirteen of the 16 patients had histologic evidence of cirrhosis, and 7 gave a history of excessive alcohol intake. Eight patients showed no evidence of HBV infection. Of these patients, six had cirrhosis and four gave a history of excessive alcohol intake. Sixteen patients were positive for α -fetoprotein, the incidence being nonsignificantly higher among the HBV-positive patients. The data lend further support to the view that HBV is etiologically related to PLCC, although other factors must also be involved. (5 refs)

79-2345 Herpes Simplex in Gynecology and Obstetrics. (Eng) Bloomfield, R. (State Univ. New York, Downstate Medical Center, Box 1216, 450 Clarkson Ave., Brooklyn, NY, 11203); Suarez, J. R.; Roque, Z. S.; Tan-taksem, P. *J Natl Med Assoc* 71(2): 161-164; 1979.

A review of 79,357 Papanicolaou smears taken at a medical center revealed that 40 patients had cellular changes characteristic of herpetic infection. Eleven were pregnant and 29 were gynecologic patients. Four of the 40 patients also had cervical dysplasia. None of the 341 smears positive

for carcinoma of the cervix showed evidence of herpes. However, after the study was concluded, one patient with carcinoma in situ and herpes was seen. A parallel survey revealed that three infants died from disseminated herpes infections between 1972 and 1976. There is evidence in the literature to suggest a definite relationship between herpes simplex virus type 2 (HSV-2) and cervical cancer. HSV-2 can transform embryo fibroblasts in vitro, and it has been isolated from a cell line derived from carcinoma in situ. Higher titers of HSV antibody have been detected in patients with dysplasia, carcinoma in situ, and invasive carcinoma. (23 refs)

79-2346 The Orderliness of Cell Proliferation and Cell Differentiation in Relation to Kinetic Heterogeneity in Mouse Bone Marrow. (Eng) Shackney, S. E. (Clinical Pharmacology Branch, Div. Cancer Treatment, NCI, Bethesda, MD, 20014). *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 789-804; 1978.

Kinetic studies of transverse sections of male NIH mouse femoral marrow produced new information on hematopoietic cell proliferation and differentiation. A model was proposed that features a small fraction of rapidly proliferating stem cells in the subendosteal region, with central migration and growth retardation of many of these cells. Migrating cells may either differentiate or serve as a slowly proliferating reserve pool. The model features population size-dependent feedback control and cytomorphological correlates. The most rapidly proliferating cells are among the largest cells in the population; of these, the premitotic cells are the largest. As cells spiral through progressively longer cycles, they do not quite double in volume between divisions. This results in small av cell volumes among the slowly proliferating cells. (42 refs)

79-2347 Lymphoid Neoplasia Following Connective Tissue Disease. (Eng) Banks, P. M. (Dept. Surgical Pathology, Mayo Graduate Sch. Medicine, Rochester, MN); Witrak, G. A.; Conn, D. L. *Mayo Clin Proc* 54(2): 104-108; 1979.

A retrospective review of 29 patients seen between 1965 and 1975 was undertaken to determine whether there are distinctive histopathologic features of the lymphoid neoplasms that occur in patients with previous connective tissue disease [mainly rheumatoid (19) and psoriatic (4) arthritis]. The types of neoplasm included Hodgkin's disease (2 cases), diffuse large-cell lymphoma (11), nodular poorly differentiated lymphocytic lymphoma (1), diffuse poorly differentiated lymphocytic lymphoma (1), diffuse well-differentiated lymphocytic lymphoma (1), and chronic lymphocytic leukemia (6). Twenty-two cases showed neither immunoblastic nor plasmacytoid features. The time interval between the onset of connective tissue disease and that of lymphoid neoplasia in 29 patients ranged from 4 mo to 63 yr (mean, 15.4 yr). At

the time of diagnosis of the neoplasia, the connective tissue disease was inactive in 11 patients, mildly active in 8, and moderately or severely active in 10. The data fail to confirm a relationship between lymphoid proliferations with immunoblastic morphology and connective tissue diseases. (17 refs)

- 79-2348 Lymphoma and Rheumatoid Arthritis (Letter to Editor).** (Eng) Isomaki, H. (Rheumatism Foundation Hosp., 18120 Heinola 12, Finland); Hakulinen, T.; Joutsenlahti, U. *Lancet* 1(8112): 392; 1979.

The incidence of malignancies in Finnish rheumatoid arthritis (RA) patients was higher than that expected in men (407 vs 354.1) but as expected in women (795 vs 783.8). The incidence of leukemia, lymphoma, Hodgkin's disease, and myeloma was 130, significantly higher ($p < 0.001$) than that expected (59.6). The continuous immunological stimulation in RA could cause proliferation and malignant transformation of some clones of immunologically competent cells. Immunodeficiency might also be involved. (3 refs)

- 79-2349 A Cluster of Osteogenic Sarcomas in Time and Space.** (Ger) Sauer, E. (I. Mediz. Klinik der Techn. Universitat, Ismaninger Strasse 22, D-8000 Munich, 80, W. Germany); Fink, U.; Theiss, W.; Rastetter, J. *Munch Med Wochenschr* 121(10): 343-344; 1979.

Four cases of osteogenic sarcoma (OGS) were diagnosed within 10 mo in people living within 17 kilometers of each other. This is believed to be the first report of a cluster of OGS in both space and time. The tumors occurred in two brothers who shared a house, and in two unrelated girls who were friends of the brothers. The first sarcoma (Case I) was found in a 21-yr-old man who presented with a swelling below the knee. An OGS of the head of the tibia was diagnosed histologically. He remains recurrence-free 6 yr after amputation was performed. Five months after the diagnosis of OGS in this patient, his 16-yr-old brother (Case II) presented with a swollen knee. Symptomatic treatment was given for 2.5 mo without improvement. OGS of the distal head of the femur was diagnosed by x-rays and by histologic criteria after amputation. Lung metastases were found 3 mo after surgery, and the patient died 4 mo later with multiple lung metastases. Case III involved a 13-yr-old girl who went to school with a brother of Cases I and II. She experienced sudden pain in a knee joint 10 mo after the diagnosis of Case I. A histological diagnosis of OGS was made 1 mo later. She died with lung metastases 1 yr later. The fourth OGS was diagnosed in a 17-yr-old girl who experienced knee pain 5 mo after the diagnosis of Case I. She was treated with radiation, amputation, and chemotherapy but died with lung metastases 2 yr later. The clustering of these cases suggests the action of an infectious agent in development of OGS. (no refs)

- 79-2350 Scar Cancer of the Lung. Increase Over a 21 Year Period.** (Eng) Auerbach, O. (Veterans Admin. Hosp., E. Orange, NJ, 07019); Garfinkel, L.; Parks, V. R. *Cancer* 43(2): 636-642; 1979.

The incidence of peripheral lung tumors related to scars among 7,629 autopsies performed in one hospital during 1955 through 1975 was studied. Lung cancer was found in 1,186 cases, 82 of which were peripheral cancers associated with scars. The number of scar cancers increased progressively from 1.8% of all lung cancers during 1955 through 1959 to 15.9% during 1970 through 1975. Forty-five percent of all peripheral lung cancers originated in a scar, with most of the scar cancers being classified as adenocarcinomas. Of the scar cancers, 56.1% were associated with an infarct, 23.2% with tuberculosis, 1.2% with granulomas, and 1.2% with asbestosis. The upper lobes of the right and left lungs were involved almost equally, and they contained 76.8% of all scar cancers. Among smokers the percent of scar cancers did not increase with the number of cigarettes smoked, and there was no apparent correlation with occupational category or with age at death. The most common sites of metastasis of all peripheral tumors (including scar tumors) were the regional lymph nodes, adrenals, liver, brain, bone, and distal lymph nodes, in that order. (23 refs)

- 79-2351 Primary Hemochromatosis and Cancer of the Esophagus.** (Spa) Curto Cardus, J. A. (Servicio de Patologia Digestiva 'A', Hospitalet de Llobregat, Barcelona, Spain); Varas Lorenzo, M. J.; Novell Sala, V.; Sirvent Calvera, J. *Rev Esp Enferm Apar Dig* 54(3): 279-288; 1978.

In a series of 211 patients with esophageal cancer, an association between esophageal cancer and primary hemochromatosis was found in 2 men (aged 75 and 51 yr, respectively). They were heavy drinkers, and one was also a heavy smoker. Both were diagnosed with differentiated keratinizing squamous epithelial carcinoma. Pulmonary tuberculosis and esophageal varices were also found in one of the men. This is the first reported association of primary hemochromatosis and esophageal cancer. (21 refs)

- 79-2352 Gastric Carcinoma and Previous Peptic Ulceration.** (Eng) Ellis, D. J. (Queen Elizabeth Hosp., Queen Elizabeth Medical Centre, Edgbaston, Birmingham, England); Kingston, R. D.; Brookes, V. S.; Waterhouse, J. A. *Br J Surg* 66(2): 117-119; 1979.

The incidence of gastric carcinoma patients that had a previously diagnosed or suspected peptic ulcer was determined by an analysis of two English studies. These studies were the West Midlands Gastric Chemotherapy Trial (1974-1976) and a retrospective study of patients presenting to the United Birmingham Hospitals with gastric carcinoma during 1958-1962 and 1968-1972. Of the total 1,026 patients, 55 had previously

undergone surgery for duodenal ulcer. A further 33 patients had a duodenal ulcer confirmed at the time of operation for carcinoma, at postmortem, or by previous radiological studies. The confirmed incidence of previous duodenal ulcer was therefore 8.6%. In addition, 51 patients had a history of dyspepsia typical of duodenal ulcer at least 5 yr before the onset of symptoms referable to carcinoma. The mean time interval between surgery for a duodenal ulcer and the development of gastric carcinoma was much longer following a partial gastrectomy (mean 24 yr) than following vagotomy and drainage (6 yr). Only 12 patients had evidence of gastric ulcer. (27 refs)

- 79-2353 Diet and Large-Bowel Cancer in Three Socio-economic Groups in Hong Kong (Letter to Editor).** (Eng) Hill, M. (Central Public Health Lab., London NW9, England); MacLennan, R.; Newcombe, K. *Lancet* 1(8113): 436; 1979.

A Hong Kong study demonstrated that colorectal cancer mortality was positively correlated with socioeconomic group and that the incidence among men in the highest income group was over twice that among men in the lowest income group. Fecal bile acid concentration was also correlated with socioeconomic group. The high-income group consumed more food of all types and higher amounts of fiber than the low- and middle-income groups. (19 refs)

- 79-2354 Mortality for Stump Cancer after Gastric Resection for Peptic Ulcer.** (Eng) Cheli, R. (Dept. Gastroenterology, Inst. Oncology, Ospedali Civili Genova, Genoa, Italy); Santi, L.; Molinari, F.; Ciancamerila, G.; Puntoni, R. In: *Prevention and Detection of Cancer. Part II. Detection. Vol. 1. High Risk Markers. Detection Methods and Management.* Nieburgs, H. E., ed. (New York: Marcel Dekker): 1299 pp.; 93-96; 1978.

The incidence of gastric stump cancer in patients who had undergone partial gastrectomy for gastric (337 patients) or duodenal (180 patients) ulcer between 1948 and 1967 was evaluated statistically. The observed mortality rate for gastric stump cancer was 7/337 patients operated on for duodenal ulcer (vs 4.1 expected) and 9/180 patients operated on for gastric ulcer (vs 3.9 expected). Compared with the general population aged > 45 yr, mortality from gastric cancer was significantly increased among patients who had undergone resection for gastric ulcer and nonsignificantly increased among patients who had undergone resection for duodenal ulcer. When the case material was analyzed following subdivision into person-years by age group, there was a highly significant increase in mortality from gastric stump cancer in both patient groups. The data support the hypothesis that the epithelial metaplasia developing early in a resected stomach may represent a condition similar to that of atrophic gastritis, both conditions being associated with a high risk of cancer. (9 refs)

- 79-2355 A Prospective Study of the Relationship Between Benign Breast Diseases and Breast Carcinoma.** (Eng) Coombs, L. J. (Div. Biostatistics and Epidemiology, Georgetown Univ. Sch. Medicine, Washington, DC, 20007); Lilienfeld, A. M.; Bross, I. D.; Burnett, W. S. *Prev Med* 8(1): 40-52; 1979.

Using a prospective approach, 747 women (15-69-yr old) diagnosed with benign breast disease (BBD) during 1957-1965, and a matched control group were followed for subsequent breast cancer (BC) development. The age-adjusted cancer mortality rate was 1.4 times higher in the BBD group than in the controls, and the age-adjusted BC mortality rate was 4.7 times higher. The BBD group also had a higher incidence rate for all cancers combined than the control group. The relative risk of BC among women with BBD was 3.0 compared with the control women. Similar to the mortality data, the differences in the overall incidence of cancer were primarily due to the higher incidence of BC in the BBD group, since the incidence of cancers other than BC was similar in the two groups. In the BBD group, women having their natural menopause at age 50 or later had a relative BC risk of 9.6. The risk associated with BBD among women having natural menopause prior to age 50 was 3.7, compared with 2.5 among women without BBD having natural menopause at age 50 or later. The relationship between BBD and BC is probably indirect, in that both BBD and BC may be the result of a similar abnormal hormonal status. BBD may simply be an earlier manifestation of this abnormal state. (34 refs)

- 79-2356 Incidence of Malignant Neoplasms of All Types in Patients with Graves' Disease.** (Eng) Munoz, J. M. (Section Publications, Mayo Clinic, 200 First St. SW, Rochester, MN, 55901); Gorman, C. A.; Elveback, L. R.; Wentz, J. R. *Arch Intern Med* 138(6): 944-947; 1978.

The incidence of malignancy among 342 Olmsted County, Minnesota residents diagnosed with Graves' disease between 1935 and 1967 was determined. During 4,736 person-years of observation, 32 malignancies were diagnosed; 24 cases were expected and the difference is not significant. Four cases of breast carcinoma were found vs five expected. Other tumor sites were cervix (5), uterus (2), rectosigmoid colon (3), stomach (2), larynx (2), and lung (2). There were three cases of leukemia, and in nine other sites one cancer each was recorded. There was a slightly higher than expected incidence of malignancy in patients who had received ¹³¹I therapy; this finding requires further study in a larger patient population. Among patients who received thyroid hormone, the observed incidence of breast cancer was not significantly different from the expected incidence in this population. (29 refs)

- 79-2357 Statistics of Leukemia Morbidity in Krakow Province, Poland, in 1951-1968.** (Rus) Ianitskii, K. (Hematological Clinic, Inst. Therapy, Krakow, Poland);

Slivchinskaia, B. *Probl Gematol Pereliv Krovi* 24(3): 38-40; 1979.

Between 1951 and 1968, leukemia was diagnosed in 1,846 patients in the province of Krakow, Poland. Calculation of the morbidity rates (per 100,000) for various variants of leukemia in the total population and in the age groups <15, 15-44, and >45 yr showed that there was a significant increase in the incidence of chronic myeloid leukemia (from 0.5 in 1951 to 2.4 in 1968), chronic lymphoid leukemia (from 0.8 to 3.8), and acute leukemia (from 1.1 to 5.33). Overall leukemia morbidity was increased in the age groups 15-44 and >45 yr (from 1.5 to 4.68 and from 3.8 to 6.24, respectively), but it was decreased in the <15-yr-old age group (from 2.7 to 1.42). (20 refs)

79-2358 Burkitt's Lymphoma in Ghana: Urban-Rural Distribution, Time-Space Clustering and Seasonality. (Eng) Biggar, R. J. (Burkitt's Tumor Project, P. O. Box 194, Accra, Ghana); Nkrumah, F. K. *Int J Cancer* 23(3): 330-336; 1979.

Epidemiologic data from 236 patients with Burkitt's lymphoma (BL) and 103 patients with non-Burkitt's lymphoma (NBL) seen between 1970 and 1975 at a hospital in Accra, Ghana, are presented. The av age for both BL and NBL patients was 7-8 yr. The male:female ratio was 1.7:1 for BL and approx 1:1 for NBL. One hundred and three of Ghana's 141 census districts were represented in the study group. There was no apparent relationship between case distribution and rainfall, and there was no seasonal variation in date of onset of symptoms or referral date. No evidence of time-space clustering was obtained. Two observations suggested a higher incidence of BL among rural vs urban populations: there were lower referral rates from all areas of >10,000 population compared with more rural communities, and there were more BL referrals than NBL referrals from small communities. Significantly more BL patients than NBL patients had fathers whose occupation was farming. There were no other significant differences related to social or economic factors. The higher risk of BL among rural dwellers is consistent with severe malaria being a factor in the etiology of BL. (18 refs)

79-2359 Incidence of Malignant Lymphoma in Hawaii. (Eng) Oishi, N. (Cancer Center Hawaii, Univ. Hawaii, Honolulu, HI); Rashad, M. N. *In: Prevention and Detection of Cancer. Part II. Detection. Vol. 1. High Risk Markers. Detection Methods and Management.* Nieburgs, H. E., ed. (New York: Marcel Dekker): 1299 pp.; 75-79; 1978.

The incidences of malignant lymphoma among the racial groups living in Hawaii during 1968 through 1972 were compared. The av annual age-race-adjusted incidence rate per 100,000 for non-Hodgkin's lymphoma was 4.9 for men and 4.6 for women. The incidence rate per 100,000 for Hodgkin's

disease was 2.4 for men and 1.6 for women. Hawaiians and Caucasians had higher incidence rates than other racial groups for Hodgkin's disease and non-Hodgkin's lymphoma and higher death rates than other racial groups for Hodgkin's disease. Filipinos had the highest death rates for the non-Hodgkin's lymphomas. The male:female ratio for non-Hodgkin's lymphoma varied from 0.2 for the Chinese to 1.6 for the Filipinos, and the ratio for Hodgkin's disease varied from 1.2 for the Japanese to 3.4 for the Hawaiians. Hawaii provides a good location for studying the epidemiology of certain types of malignancy. (15 refs)

79-2360 The Natural History of Oral Leukoplakia. (Eng) Mehta, F. S. (Basic Dental Res. Unit, Tata Inst. Fundamental Res., Homi Bhabha Road, Bombay 400 005, India); Hamner, J. E.; Pindborg, J. J. *In: Prevention and Detection of Cancer. Part II. Detection. Vol. 1. High Risk Markers. Detection Methods and Management.* Nieburgs, H. E., ed. (New York: Marcel Dekker): 1299 pp.; 83-91; 1978.

The natural histories of oral leukoplakia (LP), other possible oral precancerous lesions, and oral cancer were studied in an epidemiologic survey of 50,915 adults in India. The incidence rate for LP was 2.1/1,000 men and 1.6/1,000 women, the peak incidence rate being in the age group 55-64 yr among men and in the age group 45-54 yr among women. The incidence was zero among individuals who did not use tobacco and was highest (5.3/1,000) among those who both chewed 'pan' (a combination of betel leaf, lime, areca nut, and tobacco) and smoked 'bidi' (coarse tobacco rolled in a dry temburni leaf). Among tobacco users, bidi smokers exhibited the lowest incidence rate (1.0/1,000). Ten oral cancers (squamous cell carcinoma) were detected among individuals with LP; four were found among those with no oral lesions. The rate of malignant transformation of LP was zero among those aged <35 yr, 5.5/1,000 among those aged 35-54 yr, and 13.7/1,000 among those aged ≥55 yr. The rate of malignant transformation was twice as high for women (11.1/1,000) as for men (5.1/1,000) and twice as high for tobacco chewers (11.5/1,000) as for those who chewed and smoked (6.4/1,000). Malignant transformation was not observed among those who only smoked. The data suggest that LP's associated with different tobacco habits may have different natural histories. (5 refs)

79-2361 A Methodological Investigation of Fatal Disease Risks in a Large Industrial Cohort. (Eng) Decoufle, P. (Environmental Epidemiology Branch, NCI, Bethesda, MD, 20014); Thomas, T. L. *J Occup Med* 21(2): 107-110; 1979.

Proportionate mortality analyses of 2,843 deaths among white male workers employed at a single large industrial

plant during 1938-1967 were performed to examine variations in estimates of fatal disease risks between deceased retirees (retiree deaths) or workers who died within 1 yr of last employment at the plant (active deaths) and workers who died at least 1 yr after leaving the plant (other deaths). The major potential hazardous exposure in the plant was oil mist. Risk estimates were based on the proportionate mortality ratio (PMR) of observed deaths to age- and calendar year-adjusted expected deaths derived from general population mortality. When the results for specific malignant neoplasms were analyzed, the PMR's for most site categories were similar for the active and retiree groups combined and the other group. However, the results for respiratory cancer indicate about a 50% increase among active and retiree deaths (PMR = 1.58) and near expected mortality in the other group (PMR = 1.08). When the results for persons dying within 1 yr of last employment were analyzed separately, a 25% increase in the relative frequency of cancer deaths was seen that might suggest that this subgroup was at special risk of cancer. However, the PMR's overstate the true risk for actively employed workers, since their mortality rate is generally lower than that of the general population. In any event, these results may indicate the expected magnitude of cause-specific PMR's in an industrial population with no extraordinary fatal disease risks. Thus, in examining cancer risks among actively employed workers using the PMR approach, it may be more appropriate to judge the observed PMR for total cancer in relation to an expected PMR greater than unity (possibly in the neighborhood of 1.25). This would imply that PMR's for cancer may have to be unusually high before one can conclude that a real increase in risk exists. (17 refs)

- 79-2362 Does Driving Cause Cancer and Diabetes?** (Eng) Robinson, A. A. (16 Quayle St., Sandy Bay, Hobart, 7005 Tasmania, Australia). *Med Hypotheses* 5(1): 175-184; 1979.

The relationship between deaths due to lung cancer, diabetes, and breast cancer and parameters representative of the influence of motor vehicle travel was examined using Australian data for the period 1920-1972. An examination of the correlation between numbers of deaths due to the three diseases and motor vehicle usage per 100,000 of population revealed that these diseases are directly linked to vehicle travel rather than to the effect of pollution. Vehicle travel may produce effects on the circulatory or nervous system that are common to the three diseases. It is hypothesized that the process of traveling in a motor vehicle, particularly driving, entails the covering of distance with minimal expenditure of body energy. In the human body, the perception of motion is controlled mainly by the eye. Having received visual information, the brain controls the supply of fuel for activities such as walking or running. If body energy is used for these activities, the level of unburned fuel in the blood is minimal. However, traveling without the expenditure of energy overloads the mechanism of control and gives rise to abnormally high levels of glucose,

fatty acids, etc, in the blood, which could be related to the increased deaths due to lung and breast cancer and diabetes. A study that partially support this hypothesis is summarized. (5 refs)

- 79-2363 A Survey of Neoplastic Disease in Oklahoma Native American Aborigines.** (Eng) Skye, G. E. (Oklahoma Medical Res. Foundation, Oklahoma City, OK); Hampton, J. W. In: *Prevention and Detection of Cancer. Part II. Detection. Vol. 1 High Risk Markers, Detection Methods and Management.* Nieburgs, H. E., ed. (Marcel Dekker, Inc.: New York): 1299 pp.; 47-56; 1978.

The incidences of neoplastic and other diseases among the white and native American (American Indian) populations of Oklahoma were compared for the years 1955 through 1959 and 1970 through 1974. The white population of Oklahoma comprises 90% of the total. During the 20-yr period, there was no change in the cancer incidence rate among the Indians. The cancer mortality rate among the Indians was only 68% of that among the white population: death from pulmonary, breast, esophageal, rectal, and intestinal cancers occurred less frequently among Indians than whites; death from stomach cancer occurred at approx the same rate; and death from cervical cancer occurred two times more frequently among the Indians. During 1955-1959, cervical cancer mortality was 3.3 times more frequent among Indians than among whites, whereas during 1970-1974, the cervical cancer mortality rates were approx equal in the two populations. Lung cancer mortality increased in both populations over the 20-yr period, but the increase was only 0.5-fold among the Indians compared with 2.5-fold among the whites. The results suggest that the long association of the North American Indian with tobacco may not have an ethnic protective factor. (5 refs)

- 79-2364 Tumours in Iceland. I. Malignant Tumours of Skin--A Histological Classification.** (Eng) McKnight, C. K. (Dept. Pathology, Univ. Iceland, Reykjavik, Iceland); Magnusson, B. *Acta Pathol Microbiol Scand (A)* 87(1): 37-44; 1979.

To investigate the pattern and incidence of primary skin malignancies in Iceland, 485 primary malignant skin tumors submitted for histologic diagnosis in Iceland during 1955 to 1974 were typed according to the World Health Organization classification. Of the tumors in men, 66.8% were basal cell carcinomas (BCC), 22% were squamous cell carcinomas (SCC), and 7.2% were malignant melanomas (MM). Of the tumors in women, 66.9% were BCC, 20.8% were MM, and 10.2% were SCC. The male:female ratio for all skin tumors was 1.2:1. The commonest sites for BCC and SCC were the head and neck, followed by the trunk for BCC and the hand for SCC. The commonest site for MM was the lower limb, followed by the head and neck. Primary skin malignancies

were uncommon before middle age, but they increased sharply to a max of 107/100,000 among women and 150/100,000 among men in the eighth decade of life. The incidence of BCC among women increased significantly from 1955-1964 to 1965-1974. There were no other significant changes in incidence. The pattern observed conforms to the established pattern of a decrease in incidence associated with increased latitude and decreased exposure to direct sunlight. The similarity in the rates for men and women suggests that length of exposure is more erratic in inducing malignancy at a low intensity of radiation than at a high intensity. (12 refs)

- 79-2365 The Role of Demographic Risk Factors in Carcinogenesis.** (Eng) Rose, E. F. (Toxicology Dept. Natl. Inst. Nutritional Disease, South African Medical Res. Council, P.O.B. 192, East London 5201, South Africa). In: *Prevention and Detection of Cancer. Part II. Detection. Vol 1. High Risk Markers. Detection Methods and Management.* Nieburgs, H. E., ed. (Marcel Dekker, Inc.: New York): 1299 pp.; 25-45; 1978.

Some of the demographic risk indicators that might participate in promoting esophageal carcinogenesis in the Transkei, southern Africa, are defined. Significantly increased rates of esophageal cancer, based on observed vs expected incidence, were found in association with high population density, elevations between 1,000 and 3,000 ft above sea level, Beaufort sedimentary strata, leached-out soil, low rainfall, and Eastern Province thorn veld and high veld-sourveld-dohne veld types. The incidence rates were lowest in areas of low population density and high rainfall and in those areas covered by dolderite. The sex and age distribution were not significantly different in low- and high-incidence areas. (17 refs)

- 79-2366 Multiple Primary Cancers Involving the Esophagus and the Head and Neck Region.** (Jpn) Ikeda, H. (Dept. Radiology, Osaka Univ. Hosp., Osaka, Japan); Miyata, Y.; Masaki, N.; Shigematsu, Y.; Inoue, T. *Gan No Rinsho* 25(2): 84-88; 1979.

Among the total 327 esophageal carcinoma patients registered in a Japanese hospital between 1967 and 1976, 36 (34 men, 2 women; 30 aged 50-69 yr) also had primary cancers of other organs. A total of 40 sites were involved; four of the patients had three primaries. The most common site of the other primaries was the head and neck region (30 sites, 26 patients). The remaining patients had cancer of the stomach (6), skin (2), prostate (1), and kidney (1). Carcinomas of the hypopharynx (10) and oropharynx (4) generally developed before (4) or synchronously (6) with the esophageal cancer, and patients died from esophageal or pharyngeal carcinoma in equal proportions. In patients with laryngeal (7), tongue (5), and oral cavity cancers (3), the esophageal cancer followed the development of these primaries and was the usual

cause of death. Five of the stomach cancers preceded (2) or were synchronous (3) with the development of the esophageal cancer. (12 refs)

- 79-2367 Carcinoma of the Gallbladder and Extrahepatic Biliary Ducts in Rochester, Minnesota, 1935-1971.** (Eng) Maram, E. S. (Sch. Veterinary Medicine, Pahlavi Univ., Shiraz, Iran); Ludwig, J.; Kurland, L. T.; Brihan, D. D. *Am J Epidemiol* 109(2): 152-157; 1979.

The epidemiology of carcinoma of the gallbladder and extrahepatic biliary ducts in Rochester, Minnesota, was studied using the Mayo Clinic record system. Fifty-two cases of carcinoma of the gallbladder and/or extrahepatic biliary ducts were diagnosed between 1935 and 1971, 36 cases in women and 16 in men. The mean annual incidence rate/100,000 population was 4.4 (3.1 for men and 5.4 for women). Of the 16 extrahepatic bile duct tumors, all were adenocarcinomas. Of the 36 gallbladder neoplasms, 30 were adenocarcinomas, 4 squamous cell carcinomas, and 2 adenoacanthomas. The anatomic distribution of initial lesions at diagnosis differed between the sexes: 78% of those in women were in the gallbladder, vs 25% in men; extrahepatic biliary ducts were the initial site of malignancy in 69% of men and 14% of women. During the study period, the incidence rate of carcinoma of the gallbladder and extrahepatic bile ducts did not change significantly in men, but it decreased significantly in women. The incidence rate increased with age in both sexes. For the 51 known deaths, the death certificates listed carcinoma of the gallbladder and/or extrahepatic biliary ducts as the underlying cause of death in 39 cases and as a contributory cause in 3. The frequencies of gallstones in women (75%) and men (62%) were significantly higher than expected. (20 refs)

- 79-2368 Doubts About Carpet Factory-induced Colonic Cancer (2 Letters to Editor).** (Eng) Wen, C. P. (17611 Turtle Creek, Houston, TX, 77090); Tsai, S. P.; Vobecky, J.; Devroede, G. *Gastroenterology* 76(3): 656-657; 1979.

Six specific criticisms are made of data collection and misclassification in an article concerning the high risk of colorectal cancer in carpet factory workers. In response, data are presented that substantiate a relative risk, during 1971-1975, of 9.6 for colorectal cancer in the population of workers in a carpet factory. (1 ref)

- 79-2369 Carcinoma of the Colon: Epidemiology, Etiology, Diagnosis, and Treatment.** (Eng) Diggs, C. H. (Dept. Medicine, Univ. Maryland Sch. Medicine, 22 South Greene St., Baltimore, MD, 21201). *Am J Med Sci*

277(1): 4-16; 1979.

The epidemiology, etiology, diagnosis, and treatment of colon cancer (CC), the second most common malignancy (after skin cancer) in men and women combined, are reviewed. Two case reports that typify the clinical presentation of CC are presented. Peak incidence occurs between age 50-70. Patients may present with a variety of symptoms, and these symptoms can usually be related to the site of involvement. A right-sided abdominal mass may be the presenting feature of right-sided tumors, constipation or change in stool caliber that of left-sided tumors. Other common symptoms are bloody stools, diarrhea, abdominal pain, tenesmus, mucus in stools, anorexia, and wt loss. However, many patients are symptom-free and have their disease detected on routine exam. CC is suggested to be a disease of Western civilization, since its incidence is much greater in Western Europe and the US than in African countries or Japan. Both fat intake and fiber intake probably act together or independently to cause the increased incidence of CC in Western countries. Compounds known to induce CC in laboratory animals are listed, as are substances that modify these chemically induced tumors. Disulfiram, selenium, sodium diethyl dithiocarbamate, and several pesticides appear to decrease the number of CC produced by carcinogens. It is postulated that intake of high amounts of dietary fat increases the level of cholesterol in the bile as well as the amount of bile acids. These compounds then travel to the large intestine where they are acted upon by intestinal bacteria with enzyme activities under dietary control. As a result, carcinogens that act directly on the bowel mucosa may be formed. Dietary fiber may also interact in some fashion. Methods of screening high-risk populations are described. (62 refs)

- 79-2370 A Case-Control Study of Relationships of Diet and Other Traits to Colorectal Cancer in American Blacks.** (Eng) Dales, L. G. (Dept. Medical Methods Res., Permanente Medical Group, 3700 Broadway, Oakland, CA, 94611); Friedman, G. D.; Ury, H. K.; Grossman, S.; Williams, S. R. *Am J Epidemiol* 109(2): 132-144; 1979.

Ninety-nine black patients (52 women, 47 men) with colorectal adenocarcinoma and 280 matched controls from hospitals and multiphasic health checkup clinics were interviewed about past dietary habits and other traits. Colon cancer patients (72) tended to report less frequent use of foods with at least 0.5% fiber content than did their controls. This relationship, although small and not statistically significant, showed a consistent dose-response gradient, appeared in both case-hospital control and case-multiphasic health checkup control comparisons, and could not be accounted for by the effects of other variables. Colon and rectosigmoid junction cancer patients (77) tended to have eaten foods with at least 5% saturated fat somewhat more often than controls. When consumption of these two groups of foods was considered in combination, significantly more colon cancer patients than controls reported a high-saturated fat foods-low-fibrous

foods eating pattern. In contrast to other studies, beef consumption showed a nonsignificant negative relationship with cancer. Statistically significant excesses were also calculated for the colorectal cancer patients in the following areas: cigar smoking of > 20 yr in men, nulliparity in women, and history of colorectal polyps. The relative excess colon cancer risk associated with the combined high-saturated fat-low-fiber dietary pattern exceeded the sum of the relative excess risks when evaluated individually, suggesting a synergistic interaction of the effects of saturated fats and low-fiber food on colon cancer risk. (31 refs)

- 79-2371 Epidemiology of Cancers: I. Cancerous Diseases of the Large Bowel.** (Eng) Schwarz, K. (Dept. Preventive and Community Medicine, Christchurch Clinical Sch., Christchurch, New Zealand); McDonald, M.; Malpress, W. *NZ Med J* 87(613): 387-390; 1978.

The pilot phase of an epidemiological study of large bowel cancer in Canterbury, New Zealand, is described. The study group comprised 312 patients diagnosed with colon cancer during 1970-1972. The main categories studied were (1) demographic factors, (2) anatomical scope of the colon cancers, (3) tumor classifications, and (4) symptoms and signs of the cancer onset and preceding disease episodes. Men outnumbered women except in two age groups, 45-49 and 70-74. Demographic characteristics were not significantly different between the colon cancer patients and the general population. Tumor classification did not seem to be of value in an epidemiological context. Anemia was present in 52.9% of the patients, rectal bleeding in 43.3%, and changes in bowel habits (constipation and diarrhea) in 80%. The major pathologies were diverticulitis (19.8%), polyps (10.8%), gallstones (9.2%), hemorrhoids (7%), cholecystitis (6.4%), and gastric ulcer, duodenal ulcer, ulcerative colitis and colitis (2.2% each). Other pathologies included thyroid disease (7.3%) and cervical cancer (3.5%). An abdominal mass was palpable. Most of the tumors were located in the sigmoid colon (38.4%), cecum (14.7%), and transverse colon (9.8%). (8 refs)

- 79-2372 Choriocarcinoma Following Term Pregnancy.** (Eng) Miller, J. M. (Southwestern Regional Center Trophoblastic Disease, Dept. Obstetrics and Gynecology, Duke Univ. Medical Center, Durham, NC, 27710); Surwit, E. A.; Hammond, C. B. *Obstet Gynecol* 53(2): 207-212; 1979.

Experience in treating 265 patients with malignant trophoblastic disease who were admitted to the Southeastern Trophoblastic Disease Center at Duke University Medical Center between July 1966 and June 1976 is reported. Twenty of these patients had choriocarcinoma following a term gestation and their survival rate was 60%, compared with a 95% survival rate for the remaining 245 patients. Previously de-

scribed risk factors of initial human chorionic gonadotropin titer of $> 100,000$ IU/24-hr urine, duration of symptoms for > 4 mo, significant prior unsuccessful chemotherapy, or cerebral or hepatic metastases identified the poor prognosis group. Postterm gestation poor prognosis patients had a significantly lower cure rate (47%) than other patients with a poor prognosis for gestational trophoblastic disease (75%; $p < 0.05$). Postterm gestation choriocarcinoma has a propensity for more extensive metastatic spread and would appear to be less responsive to conventional chemotherapy; this may be due to an altered immune response in these patients. It is suggested that an antecedent term pregnancy should be added to the previously described high-risk factors for patients with malignant trophoblastic disease. (21 refs)

- 79-2373 US Cancer Incidence and Mortality in the First Year of Life.** (Eng) Bader, J. L. (Clinical Epidemiology Branch, NCI, Rm A521 Landow Bldg., Bethesda, MD, 20014); Miller, R. W. *Am J Dis Child* 133(2): 157-159; 1979.

Data from the Third National Cancer Survey were used to evaluate the incidence of and mortality from cancer in infants aged < 1 yr between 1969 and 1971. A total of 196 tumors were diagnosed in 195 patients, the overall incidence being 183.4 per million live births. The mortality rate from cancer was 52.7 based on 2,044 deaths. The incidence was 35% higher in males than in females and 28% higher in whites than in blacks. Half of the cancers were found on the first day of life and two-thirds were found during the first week. Based on incidence, the most common tumor was neuroblastoma, followed by leukemia, kidney tumors, sarcomas, retinoblastoma, and CNS tumors. When mortality before 1 yr of age was used as an indicator of frequency, leukemia was ranked first, followed by neuroblastoma, CNS tumors, and tumors of the kidney. Differences in rank order based on mortality and incidence were due largely to differences in survival due to treatment. Cancer present at or soon after birth presents an opportunity to study causal factors that become less evident when a longer interval is involved. (27 refs)

- 79-2374 Clinical Statistics of Pediatric Urology at a Japanese Hospital from 1968 to 1977.** (Jpn) Takamatsu, M. (Dept. Urology, Wakayama Medical Coll., Wakayama, Japan); Kitagawa, M.; Morimoto, S.; Ogawa, T.; Ohkawa, T. *Acta Urol Jpn* 24(12): 1075-1081; 1978.

From 1968 to 1977, 3,789 children (2,870 males, 919 females) were treated at the urology department of a Japanese hospital. These patients comprised 15% of all the urological patients seen during this period. Congenital disorders (722 males, 76 females; 29.4%), nonspecific inflammatory diseases (438, 176; 22.6%), and functional urinary disturbances (323, 190; 18.9%) were the most common diseases. Twenty-nine of the children had tumors, 24 of which were malignant. They

included Wilms' tumor (9 patients), neuroblastoma (6), retroperitoneal lymphangioma (1), retroperitoneal teratoma (1), testicular tumors [11: embryonal carcinoma (5), adult teratoma (2), malignant teratoma (2), seminoma (1), metastatic malignant lymphoma (1)], and scrotal hemangioma (1). (13 refs)

- 79-2375 Menstrual History and Breast Cancer.** (Bul) Todorov, V. (Surgical Clinic, Res. Inst. Oncology, Sofia, Bulgaria). *Vopr Onkol* 15(4): 171-174; 1979.

To determine whether age at menarche is a risk factor for breast cancer, the menstrual histories of 564 women with a histologically confirmed diagnosis of breast cancer and 1,136 healthy women (controls) were analyzed. It was found that 11.5% of the patients began to menstruate at age of 12, compared with 1.9% of the controls. Late onset of menarche (after 17 yr) was found in 1.4% of the patients, compared with 4.7% of the controls. Prolonged (> 35 yr) active function of the ovaries was recorded in 57% of the patients vs 40.0% of the controls. (24 refs)

- 79-2376 Demographic Investigation of Mammary Carcinoma in Northern Sweden.** (Eng) Larsson, L. G. (Center Oncology, Univ. Hosp., S-901 85 Umea, Sweden); Sandstrom, A.; Cumberbatch, J.; Johnsson, M. *Acta Radiol [Oncol]* (Stockh) 17(6): 497-509; 1978.

The age-standardized incidence rates for female breast carcinoma during 1959-1971 were calculated for the three northernmost counties in Sweden and their municipalities. The age-adjusted incidence rate for the entire region was 58.8 compared with 76.3/100,000 for the whole of Sweden. However, very great variations existed between different municipalities. In 11/35 municipalities, the rates differed significantly from the incidence for the entire region, and in 9 of these municipalities the deviation was towards a lower incidence. Age-specific incidence curves were compared for high-incidence, medium-incidence, and low-incidence municipalities. All curves showed a peculiar hook around the age of menopause. For the low-incidence municipalities a bimodal curve was obtained. The most marked difference between low-incidence and high-incidence municipalities concerned the postmenopausal age. For the period 1959-1971, the crude incidence increased by 3%/yr and the age-adjusted incidence increased by 1.5%/yr, both in the whole of Sweden and in the three counties. Therefore, about half of the increase in incidence rate could be explained by the changing age distribution. Other factors must account for the remainder of the increase. (31 refs)

- 79-2377 Ovarian Cancer. Incidence and Case-Control**

79-2377 Study. (Eng) Annegers, J. F. (Section Medical Statistics, Mayo Clinic, 200 First St. S.W., Rochester, MN, 55901); Strom, H.; Decker, D. G.; Dockerty, M. B.; O'Fallon, W. M. *Cancer* 43(2): 723-729; 1979.

The incidence of ovarian cancer in Rochester, Minnesota, during 1935-1974 was determined, and potential risk factors for epithelial ovarian cancer were evaluated based on 116 ovarian cancer patients and 464 matched controls. The incidences of ovarian cancer, adjusted for age and population at risk, were 25.0, 22.9, and 17.8 per 100,000 during 1945-1954, 1955-1964, and 1965-1974, respectively. The age-adjusted incidence rate was 22.6/100,000 during 1935-1944. The incidence rates rose sharply until approx age 60, then leveled off. There was no apparent association between the incidence of breast and ovarian cancer. Among the 116 epithelial ovarian cancer patients and 464 controls, nulliparity, with a relative risk of 1.8, was the only significant risk factor for ovarian cancer. Age at menopause, obesity, hypertension, prior pelvic radiation, and prior exogenous estrogen usage were not significant risk factors. The ovarian cancer patients had a significantly lower frequency of prior hysterectomy and of unilateral oophorectomy than the controls. Thus, the available data seem to support previous findings that women who have had a hysterectomy but retain at least one intact ovary are at lower risk of subsequent ovarian cancer than those who have not had a hysterectomy. (21 refs)

79-2378 Epidemiology of Carcinoma In Situ of the Cervix Uteri. (Eng) Sachs, H. (Universitäts-Frauenklinik, D-6650 Hamburg, W. Germany). In: *Cervical Pathology and Colposcopy. Selected Papers from the Second World Congress of Cervical Pathology and Colposcopy held in Graz, Austria, 15-18 October 1975.* Burghardt, E.; Holzer, E.; Jordan, J. A., eds. (Stuttgart: Georg Thieme Publishers): 146 pp.; 119-122; 1978.

A review of epidemiological studies of carcinoma in situ of the cervix uteri in West Germany shows a higher percentage of cytologically detected carcinoma in situ cases than might be expected based on the number of women participating in routine cancer detection programs. This rate was nearly 80% in Sudwürttemberg-Hohenzollern for the year 1972 and 45% in the Saarland for the year 1973. Carcinoma in situ of the cervix uteri is predominantly detected by routine mass screening in women under the age of 50. A review of 10,425 cases of carcinoma in situ of the cervix uteri observed throughout the world in women under the age of 30 yr shows that the incidence of this disease in this age group ranges from 9.1% to 17.6%. It is suggested that women, particularly older women, should be encouraged to participate in routine mass screening and that women with specific risk factors for cervical cancer should be identified and persuaded to have routine gynecologic examinations. (11 refs)

79-2379 Relationship Between the Age of the Beginning of Sexual Activity and Socio-Economic Status in the Incidence of Carcinoma of the Uterine Cervix. (Eng) de Almeida, A. C. (Catholic Medical Sch., Porto Alegre, Brazil); Callegari, T. R. In: *Prevention and Detection of Cancer. Part II. Detection. Vol. 1. High Risk Markers. Detection Methods and Management.* Nieburgs, H. E., ed. (New York: Marcel Dekker): 1299 pp.; pp. 65-74; 1978.

The relationships between age at the beginning of sexual activity, socioeconomic status (SES), and cervical cancer were studied in 3,920 Brazilian women who had undergone cytologic and/or colposcopic examination of the uterine cervix. The incidence of cervical cancer was 83/3,920 total study population; 46/1,667 women of low SES and 37/2,253 women of high SES. Significantly more women of low SES (55.1%) engaged in sexual activity before 20 yr of age than did women of high SES (44.9%). The incidence of cervical cancer was significantly higher among women of low SES who began sexual activity before the age of 20 (74.5%) than among those of low SES who began sexual activity after the age of 20. There was no significant difference in the incidence of cervical cancer when related to age of first sexual activity in women of high SES. (16 refs)

79-2380 Epidemiology--Some New Aspects on the Prevention of Cervical Cancer. (Eng) Pauli, H. K. (Chefarzt der Geburtshilflich, Gynakologischen Abteilung am Krankenhaus, Elim, Hohe Weide 17, D-2000 Hamburg 19, W. Germany). In: *Cervical Pathology and Colposcopy. Selected Papers from the Second World Congress of Cervical Pathology and Colposcopy held in Graz, Austria, 15-18 October 1975.* Burghardt, E.; Holzer, E.; Jordan, J. A., eds. (Stuttgart: Georg Thieme Publishers): 146 pp.; 111-119; 1978.

Social characteristics were analyzed among 756 women in West Germany who were suffering from squamous carcinoma of the cervix or its preliminary stages. The incidence of carcinoma of the cervix was found to be more frequent when the following social factors appeared: no or few social contacts, no bathroom, coitus during teenage years, two or more intimate partners, two or more marriages, pregnancies, births, and birth of first child during adolescence. Women with none or only one of these factors were classified as low risk, women with two or three as medium risk, and women with more than three factors as high risk. The proportion of women with carcinoma of the cervix increased from 4.4% for low risk to 9.4% for medium risk to 15.8% for high risk. The number of women with a high number of social factors that inhibited attendance for gynecological screening increased according to the number of risk factors. (27 refs)

79-2381 Field Trials in Cervical Cancer in the R.S.A. (Eng) Muller, C. J. (Dept. Radiology, Univ. Stellenbosch, Stellenbosch, South Africa). In: *Prevention and*

Detection of Cancer. Part II. Detection. Vol. 1. High Risk Markers. Detection Methods and Management. Nieburgs, H. E., ed. (New York: Marcel Dekker): 1299 pp.; 57-63; 1978.

Preliminary results of a cervical cancer screening program among South Africans are presented. Early cases were detected by Papanicolaou smears. The results showed an inverse correlation between the incidence of cervical cancer and socioeconomic group. (11 refs)

79-2382 Cancer Epidemiology. A Continuing Series on Different Sites, Based on the New South Wales Data. Series No 6: Cancer of the Prostate and Bladder in NSW. (Eng) Ford, J. (Central Cancer Registry, Health Commission of NSW, GPO Box 4235, Sydney, NSW 2001). *Cancer Forum* (12): 475-478; 1977.

Data collected by the New South Wales Central Cancer Registry revealed that cancer of the prostate ranks second to lung cancer among the leading cancers of men in this state. In 1972, there were 535 new cases, constituting 10% of all new male cancer cases. The incidence rate rises sharply at age 60 and continues to increase with increasing age. There were 434 deaths from cancer of the prostate in 1972, making this the second leading cause of death from cancer (after lung cancer) in men. Cancer of the bladder was the sixth leading primary cancer among men in New South Wales. The total number of new cases was 292 (6% of all new male cancers), and the incidence rate was 12.7%. The male:female ratio of incidence rates for bladder cancer was 2.89:1. (no refs)

79-2383 Occupational Cancer in Men Exposed to Dust and Other Environmental Hazards. (Eng) Bross, I. D. (Roswell Park Memorial Inst., Buffalo, NY); Viadana, E.; Houten, L. *Arch Environ Health* 33(6): 300-307; 1978.

Data on a series of 14,000 cancer patients admitted to one institution between 1956 and 1965 and for whom a detailed epidemiological schedule involving occupational history and

> 75 other factors was taken prior to diagnosis were analyzed for occupational cancer risks. A number of relationships were found between occupations in which dust exposure would be suspected and cancers at particular sites. The risk of melanoma was the most widespread, being significantly elevated in five occupational groups (blacksmiths, excavators, laborers in paper manufacturing, millwrights, and roofers). The risk of stomach cancer was significantly elevated in three occupational groups (millwrights, operatives employed in the textile industry, and shoemakers), as was the risk of pancreatic cancer (laborers in miscellaneous manufacturing, operatives in paper manufacturing, and shoemakers) and cancer of the nose (brickmasons, operatives employed in the textile industry, and shoemakers). The risk of cancer of the buccal-pharyngeal cavity (shoemakers), esophagus (brickmasons, laborers in lumber industry), prostate (blacksmiths, dairy farmers), kidney (brickmasons, roofers), and bladder (dairy farmers) was significantly elevated in at least one occupational group. The findings were not significantly altered by including smoking habits or ethnic background in the analysis. (12 refs)

See also:

*(Rev.): 79-1804, 79-1805, 79-1809, 79-1810, 79-1812, 79-1821, 79-1822, 79-1824, 79-1825, 79-1826, 79-1828, 79-1829, 79-1830, 79-1842, 79-1843, 79-1844, 79-1846, 79-1854, 79-1872, 79-1875, 79-1876, 79-1879, 79-1880, 79-1881, 79-1883, 79-1884, 79-1885, 79-1886, 79-1887, 79-1888.

*(Chem.): 79-1896, 79-1898, 79-1899, 79-1910, 79-1923, 79-1928, 79-1930, 79-1932, 79-1933, 79-1968, 79-2051, 79-2052, 79-2054, 79-2082, 79-2094, 79-2095, 79-2102, 79-2103.

*(Phys.): 79-2118, 79-2121.

*(Immun.): 79-2284, 79-2293.

*(Path.): 79-2318.

MISCELLANEOUS

79-2384 A Nonlinear Stochastic Model for Optimal Estimation of Causative Factors in Cancer. (Eng)

Prasad, T. (Univ. Waterloo, Waterloo, Ontario, Canada N2L 3G1); Ibidapo-Obe, O.; Prasad, S. In: *Prevention and Detection of Cancer. Part II. Detection. Vol. 1. High Risk Markers. Detection Methods and Management*. Nieburgs, H. E., ed. (New York: Marcel Dekker): 1299 pp.; 1287-1296; 1978.

A model corresponding to the Ito-Doob nonlinear stochastic integral equations is proposed for the in vitro estimation of the causative factors for cancerous growth. The model depicts a simplified version of the essential biological concepts that underlie a cancerous state. Realistic mathematical algorithms yielding conceptually similar and explicit solution schemes and based on the innovations concept and theory of martingales are outlined. The algorithm may also provide a basis for cancer chemotherapy and compact and precise mathematicobiophysical representations for other physiological problems. The approach is interdisciplinary in character, and its utilization would depend on effective coordination between researchers from diverse disciplines. (24 refs)

79-2385 Models of Cell Surface Events During Normal and Transformed Human Cellular Adhesion In Vitro. (Eng)

Rajaraman, R. (Dept. Microbiology, Faculty Medicine, Dalhousie Univ., Halifax, Nova Scotia, Canada); Fox, R. A.; MacSween, J. M. *Ann NY Acad Sci* 312: 441-443; 1978.

It is hypothesized that patching, capping, endocytosis, and cellular locomotion are manifestations of a single process: the cell discarding foreign and unwanted materials. A molecular model of normal and neoplastic cellular adhesion in the presence and absence of serum is proposed based on the interpretation that capping is caused by abortive adhesion and does not result in locomotion. In this model, normal, but not transformed, cells have adhesion sites (A molecules) on their surface that bind to B molecules in serum. Blockage of A molecules on normal cells by binding of free B molecules is cleared by capping, whereas binding of A molecules with substratum-bound B molecules results in cellular adhesion. Transformed cells may recruit A molecules from serum to attain deformability and spreading. These cells may be defective in capping surface-bound ligands. Thus, the degree of dependence on serum for deformation and spreading may be determined by the rate at which the cell can synthesize endogenously and/or recruit exogenously A molecules. The major differences between normal and transformed cellular

adhesion and spreading appear to be the lack of adhesion sites and the lower rate of formation of adhesion sites at the active edges in the latter. (22 refs)

79-2386 Independence of Normal Phenotypic Properties and Cell Surface Receptor Mobility in Variant Cell Lines. (Eng)

Williams, R. E. (Dept. Microbiology, Molecular Biology Inst., Univ. California, Los Angeles, CA, 90024); Linsley, P. S.; Rittenhouse, H. G.; Fox, C. F.; Boone, C. W. *J Supramol Struct* 9(2): 147-156; 1978.

Three classes of variant cell lines derived from the transformed LM line were compared with the parental cells with respect to several characteristics commonly associated with malignant transformation. The LM cell line has evolved over a 35-yr period from a methylcholanthrene-treated culture of L cells into a line adapted for growth in serum-free medium. In contrast to LM, all variant lines showed an obligate serum requirement for growth and displayed phenotypic properties consistent with an increased anchorage dependence for growth. All variants were at least slightly tumorigenic in male C3H/NIH mice, although the tumors induced by the higher dilutions of variant cells tended to develop more slowly than those induced by LM. The variants were less agglutinable by concanavalin A (Con A) than was LM, but the Con A-binding sites of all variants and the parental line had identical tendencies to cluster in response to lectin treatment. Thus, the apparent mobility of Con A-binding sites is not a reliable attribute of the transformed cell, since it is easily uncoupled from other, more established indicators of transformation. (20 refs)

79-2387 Transformation-sensitive Cell Surface Protein: Isolation, Characterization, and Role in Cellular Morphology and Adhesion. (Eng)

Yamada, K. M. (Lab. Molecular Biology, NCI, Bethesda, MD, 20014); Olden, K.; Pastan, I. *Ann NY Acad Sci* 312: 256-277; 1978.

The structure, composition, function, mobility, and regulation of a transformation-sensitive glycoprotein known as cell-surface protein (CSP) or LETS (large, external, transformation-sensitive) protein were investigated with purified preparations from chick embryo fibroblasts (CEF). CSP is an adhesive protein that increases cell-cell and cell-substratum adhesiveness. Transformation of CEF results in decreased quantities of CSP due primarily to a fivefold reduction of CSP

biosynthesis, although increased proteolytic degradation and shedding from the cell surface also contribute. The decreased biosynthesis is apparently due to a fivefold reduction in translatable messenger RNA for CSP. Reconstitution of isolated purified CSP on 14 transformed chicken, mouse, rat, hamster, and human cell lines resulted in reversion to a more normal fibroblastic morphology, adhesiveness, cell-surface architecture, microfilament bundle organization, motility, and alignment at confluence. CSP did not restore growth control. The effects of CSP appear to be due to increased cell-substratum adhesion plus altered cell-cell interactions. Untransformed CEF treated with affinity-purified antibodies to CSP develop the rounded morphology characteristic of many transformed cells that are CSP-deficient. CSP is found primarily in fibrillar aggregates on the cell surface. Isolated CSP consists of highly asymmetric disulfide-linked dimers and multimers. The interchain disulfide bridges are confined to a short terminal fragment that is readily removed by trypsin. CSP and cold-insoluble globulin have similar compositions but differ in solubility and amino termini. CSP contains primarily asparagine-linked oligosaccharides that appear responsible for the concanavalin A receptor activity of CSP. Inhibition of CSP glycosylation by tunicamycin results in decreased CSP due to marked increases in its degradation rate, without inhibition of synthesis or secretion. Studies of CSP have provided insight into cellular adhesion, morphology, and social interaction and provide an approach to analyze the dynamics and regulation of protein synthesis, glycosylation, secretion, and turnover. (47 refs)

- 79-2388 Subunit Structure of Surface and Shed Large, External, Transformation-sensitive Protein of Chick Embryo Fibroblasts.** (Eng) McConnell, M. R. (Dept. Pharmacology, Harvard Medical Sch., Boston, MA, 02115); Blumberg, P. M. *Ann NY Acad Sci* 312: 418-419; 1978.

For the chick fibroblast system, quantitation after lactoperoxidase-catalyzed iodination indicated that 21.3% of total surface LETS (large, external, transformation-sensitive) protein was present as the dimer and 77.4% as the oligomer. Similar studies of shed LETS protein indicated that its subunit structure closely resembles that of surface LETS protein. Apparently, the LETS protein dimer is as stable in its attachment to the cell surface as the oligomeric form, as both seem to be released from the cell surface into the medium at similar rates. (4 refs)

- 79-2389 Chemical Composition, Gross Structure, and Organization of Transformation-sensitive Glycoproteins.** (Eng) Carter, W. G. (Biochemical Oncology, Fred Hutchinson Cancer Res. Center, Univ. Washington, Seattle, WA, 98104); Fukuda, M.; Lingwood, C.; Hakomori, S. *Ann NY Acad Sci* 312: 160-177; 1978.

Three classes of transformation-sensitive, surface-labeled

glycoproteins (gp) were detected in studies of the galactoproteins (Gap) of hamster NIL and NILpy (polyoma virus-transformed) cells. Gap a, a gp with a subunit mol wt of 230,000 (230K), was deleted in transformed cells and showed high sensitivity to exogenous treatment of cells with trypsin. In contrast, increased amount of label was found in a 130K gp (Gap b) in NILpy cells. The Gap b fraction of NILpy cells also contained a gp (Gap bT) whose mobility on gel electrophoresis was faster than that of normal Gap b. A new gp with a subunit mol wt of 170K was found to be a transformation-sensitive but protease-resistant gp. This gp was also deleted in transformed cells. The chemical composition, gross structure, and organization of these gp are presented, and their sequential extraction is illustrated. Most of the membrane and cytoplasmic proteins were extracted by sequential treatment of cells with sucrose-ATP-EDTA, followed by the zwitterionic detergent Empigen BB, whereas part of the cytoskeletal proteins, including an "actinlike protein," and essentially all Gap a remained unextracted. Subsequent urea extraction solubilized an actinlike protein that was copurified with Gap a upon affinity chromatography with a *Ricinus communis*-polyacrylylhydrazidoagarose column. A serum gp immunologically identical to Gap a has been detected in conditioned culture media; presumably, it is shed from the cells as a soluble form of Gap a (released-form Gap a). Both Gap a and gp 170K appear to be associated with particular cytoskeletal proteins. A possible association of gp 170K with an intermediate filament protein is suggested by affinity copurification and coprecipitation. Some data also suggest that Gap a and actin are associated. An interaction between membrane glycolipids and proteins extracted from the same cells is postulated. This glycolipid-ektoprotein interaction could be a molecular basis of intercellular interaction. (39 refs)

- 79-2390 A Large Glycoprotein Lost from the Surfaces of Transformed Cells.** (Eng) Hynes, R. O. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139); Ali, I. U.; Destree, A. T.; Mautner, V.; Perkins, M. E.; Senger, D. R.; Wagner, D. D.; Smith, K. K. *Ann NY Acad Sci* 312: 317-342; 1978.

Studies of the structure and functions of a large, external, transformation-sensitive (LETS) protein that is lost or greatly reduced on the surface of transformed cells are presented. Alterations in LETS protein levels at the cell surface occur upon transformation and, in normal cells, in response to growth stimulation and during the cell cycle. There appear to be differences however, between the situation in transformed cells (lower rate of synthesis, higher rate of turnover) and growing normal cells (lower rate of synthesis, no evidence for increased turnover). Readdition of LETS protein to transformed cells causes increased attachment, stronger adhesion, and greater spreading and elongation of the cells. The elevated numbers of microvilli and ruffles characteristic of many transformed cells can be reduced by the addition of LETS protein, and microfilament bundles characteristic of normal

cells can be restored. The locations of LETS protein beneath spreading and migrating cells are consistent with the hypothesis that LETS plays a role in cellular spreading and movement. It is also possible that LETS protein is involved in cell-cell adhesion. Cold-insoluble globulin (CIg) and LETS protein are closely related antigenically and structurally, but CIg is two to three times less active in promoting the attachment of transformed cells to plastic dishes. It can, however, perform similar functions regarding the adhesion of platelets. (79 refs)

79-2391 Fibronectin and the Pericellular Matrix of Normal and Transformed Adherent Cells. (Eng)

Vaheri, A. (Dept. Virology, Univ. Helsinki, 00290 Helsinki 29, Finland); Alitalo, K.; Hedman, K.; Keski-Oja, J.; Kurkinen, M.; Wartiovaara, J. *Ann NY Acad Sci* 312: 343-353; 1978.

The organization and composition of insoluble fibronectin (FN)-containing structures in layers of adherent cells are reviewed. FN appears to be a major component of a pericellular (PC) matrix that can be regarded as an in vitro equivalent of the basal laminae and connective tissue matrix. The significance of the PC matrix to normal cells and of the loss of the matrix to transformed cells is considered. PC FN is located predominantly in fibrillar structures that often mediate distant cell-cell and cell-substratum contacts. A small proportion is closely associated with the plasma membrane. In the matrix, FN is partially disulfide-bonded into complexes. Plasma transglutaminase, activated by thrombin, also cross-links external FN into high-mol-wt covalent complexes. In cultures of normal fibroblasts, PC FN displays an extensive codistribution with (pro)collagens types I and III. Transformed adherent cells show a decreased formation of the FN-collagen matrix. In normal chick embryo fibroblasts there is a dense meshwork of fibrillar matrix in which both FN and procollagen type I are present. In cultures of fibroblasts transformed with Rous sarcoma virus, little or no PC FN or procollagen is detected. The loss of the PC FN-collagen matrix during transformation may be due to decreased synthesis of the matrix components and decreased binding of these components to the cell layers. The PC matrix structure was isolated by the sequential exposure of cells to sodium deoxycholate and hypotonic buffers in the presence of protease inhibitors. Human sarcoma cells seeded on this matrix spread rapidly and assume the morphology characteristic of normal fibroblasts. These results suggest that the FN-collagen matrix in vitro may provide a model system for studies of the functions of the basal laminae and connective tissue matrix. (45 refs)

79-2392 Modulation of Cell Surface Glycocalyx: Studies on Large, External, Transformation-sensitive Protein. (Eng) Chen, L. B. (Sidney Farber Cancer Inst., Harvard Medical Sch., Boston, MA, 02115); Burridge, K.; Mur-

ray, A.; Walsh, M. L.; Copple, C. D.; Bushnell, A.; McDougall, J. K.; Gallimore, P. H. *Ann NY Acad Sci* 312: 366-381; 1978.

Studies of the large, external, transformation-sensitive (LETS) protein and its relation to cold insoluble globulin (CIg), to oncogenicity, and to collagen are discussed. LETS and CIg are similar antigenically and in their amino acid compositions. However, the N-terminal amino acids and sialic acid compositions are different, CIg migrates slightly faster than LETS protein on sodium dodecyl sulfate-polyacrylamide gels, and purified human CIg does not restore normal morphological features in transformed chick cells but chick LETS protein does. In virally transformed cell lines there is a correlation between an increase in tumorigenicity in vivo and a decrease in the percentage of cells that express LETS protein on cell-cell contact. In > 100 normal cell lines studied, four categories of LETS protein distribution were detected: (1) in the cell-substratum contact area; (2) in the cell-substratum and cell-cell contact areas; (3) in the cell-cell contact area; and (4) in some of the cell-cell contact areas. Electron microscopic studies of chick embryo fibroblasts indicate that the fibrillar structures that contain LETS protein are composed of numerous fine fibers (40-60 Å), many of which are clustered together. These studies also indicate that LETS protein distributes as a three-dimensional matrix in confluent culture and that the secretion and early fibrillogenesis of LETS protein and collagen are distinct but that in the later stages of matrix formation, they may interact in certain cell types. (39 refs)

79-2393 Differences in the Ultrastructural Localization of Fibronectin on Normal and Transformed Cells. (Eng) Furcht, L. T. (Dept. Lab. Medicine and Pathology, Univ. Minnesota Medical Sch., Minneapolis, MN, 55455); Mosher, D. F.; Wendelschafer-Crabb, G. *Ann NY Acad Sci* 312: 426-431; 1978.

Studies of fibronectin (FN) organization on normal and transformed human fibroblasts (FB) using the peroxidase-antiperoxidase method are reviewed. Human FB from low-density cell populations lacks any significant amount of extracellular components. With increasing density and cellular contacts, an extensive extracellular filamentous matrix (EFM) develops that is most pronounced at cell-cell and cell-substratum contact sites. Simian virus 40 (SV40)-transformed human FB fails to develop the EFM. Two patterns of FN localization were observed in contacted human FB: an intense reaction to the EFM and a diffuse nonstructured binding to the cell membrane. In SV40-transformed human FB, FN was detected in a patchy, diffuse, membrane-associated form that was decreased in intensity relative to the diffuse form seen in normal human FB. The EFM can be disrupted by mild trypsin digestion, but it is little affected by collagenase. SV40-transformed human cells produce much more FN than normal cells. Therefore, the fundamental perturbation that occurs on transformation may be a failure to

organize FN into an EFM. The presence or absence of an EFM composed of FN may be involved in the phenotypic characteristics of normal and transformed cells. Whether an EFM is formed in transformed cells and then degraded or is never formed is being investigated. (12 refs)

- 79-2394 Restriction and Modification Enzymes and Their Recognition Sequences.** (Eng) Roberts, R. J. (Cold Spring Harbor Lab., P.O. Box 100, Cold Spring Harbor, NY, 11524). *Gene* 4(3): 183-193; 1978.

A table is presented of 177 endonucleases known to cleave DNA at a specific sequence. Also listed are the microorganism from which an enzyme was isolated, the microorganism's source, the sequence recognized by the enzyme, the number of cleavage sites, and appropriate references. (86 refs)

- 79-2395 Cellular Transglutaminase, Growth, and Transformation.** (Eng) Birckbichler, P. J. (Biomedical Div., Samuel Roberts Noble Foundation, Inc., Ardmore, OK, 73401); Patterson, M. K. *Ann NY Acad Sci* 312: 354-365; 1978.

Transglutaminase (TGase) activity and its possible relationship to transformation were studied in cultures derived from human embryonic lung, strain WI-38, and a simian virus 40 (SV40)-transformed counterpart, WI-38 VA13A. TGase activity was higher in the normal than in the transformed lung cells and in several other paired cell systems (eg, rat liver and malignant primary and transplanted hepatoma). The enzymatic reaction product, ϵ -(γ -glutamyl)lysine, was present in greater amounts in WI-38 than in WI-38 VA12A cells. Both enzymatic activity and immunofluorescent staining with rabbit anti-TGase were greater in confluent, nongrowing normal cells. TGase activity could be increased by incubation of cells with low levels of some proteases (eg, trypsin). In WI-38 homogenates, there appeared to be an inverse relationship between growth of the cells and enzymatic activity. During rapid proliferation, enzymatic activity was low. As proliferation ceased, TGase activity increased and continued to rise for several days after confluence. It is postulated that the low enzymatic activity in transformed cell systems reflects the presence of a rapidly proliferating population. There are several similarities between TGase and fibronectin (FN): normal lung fibroblasts have higher TGase activity and bind FN; TGase activity and cell-surface FN in these cells parallel one another; proteases that cleave FN activate TGase and the time course is similar for these two phenomena. FN serves as a substrate for TGase. These findings indicate that there is a close relationship between TGase and FN. (32 refs)

- 79-2396 Flow Microfluorometric Identification of Liver Cells with Elevated Gamma-Glutamyltranspep-**

tidase Activity after Carcinogen Exposure. (Eng) Vanderlaan, M. (Biomedical Sciences Div., Lawrence Livermore Lab., Univ. California, Livermore, CA, 94550); Cutter, C.; Dolbeare, F. *J Histochem Cytochem* 27(1): 114-119; 1979.

A fluorometric cytochemical assay for γ -glutamyltranspeptidase (γ -GT) activity was developed. γ -Glutamyl-4-methoxy-2-naphthylamide was used as substrate, and the released methoxynaphthylamide was coupled with 5-nitrosalicylaldehyde to form a yellow fluorescent crystalline product within the cells. Single cell suspensions were obtained by collagenase perfusion of livers from female Simonson albino rats that had undergone two-thirds partial hepatectomy followed in some cases by a single ip injection of diethylnitrosamine (DEN, 13 mg/kg) 24 hr later. Cultured hepatoma HTC-B1 cells were used as a source of monodisperse cells for the development of flow cytometric techniques. Fluorescence (γ -GT activity) was extensive in the HTC cells, but most hepatocytes from untreated and DEN-treated hepatectomized rats were negative for γ -GT. The livers of both DEN-treated and untreated rats contained some cells that were positive for γ -GT; these subpopulations could be quantitated and sorted by flow cytometry. Five weeks after DEN treatment, the percentage of γ -GT-positive cells in the livers from DEN-treated rats was 20-fold higher than that in the livers from untreated rats. Fluorescence sorting of γ -GT-positive cells may be useful for studies of early neoplastic events in a variety of organs. (25 refs)

- 79-2397 Superoxide Dismutase in Normal and Malignant Tissues in Different Species.** (Eng) Van Balgooy, J. N. (Div. Neurosciences, City of Hope Natl. Medical Center, Duarte, CA, 91010); Roberts, E. *Comp Biochem Physiol B* 62B(3): 263-268; 1979.

Superoxide dismutase (SOD) distributions in different species were investigated electrophoretically, and isoenzyme patterns in normal and malignant tissues were compared. Brain samples from rat, mouse, guinea pig, hamster, rabbit, frog, and fish contained similar SOD activities [13.0-19.0 units (U)/mg]. Lower activities were found in malignant hamster embryo fibroblasts (8.0-10.0 U/mg and crayfish muscle (4.6-6.2 U/mg), and the highest levels were found in *Escherichia coli* (19.2 U/mg). The isoenzyme patterns differed in tissues from different species. Rat brain contained little slow-moving (Mn-containing, mitochondrial) SOD, and all tissues except crayfish and *E. coli* contained a considerable amount of cyanide-sensitive SOD. In rat brain, the hypothalamus had the highest SOD activity, the cortex the lowest. Total brain SOD activity did not differ with age in mice aged 1 day to adult, but slow-moving SOD increased with age. In general, malignant tissues appeared to have lower SOD activities than normal tissue, although the values for leukemias 5FU and P388 were in the range of those for normal lung and brain. The distribution of the Cu-containing SOD isoenzymes in tumor tissue was similar to that of normal host

tissue, but the Mn-containing SOD was barely detectable in tumor cells. (25 refs)

79-2398 Teratoma Induction in Mice and Rats in Relation to the Age of the Visceral Yolk Sac. (Eng)

Sobis, H. (Rega Inst. Medical Res., Univ. Leuven, B-3000 Leuven, Belgium); Vandeputte, M. *Eur J Cancer* 15(2): 143-151; 1979.

The morphological and biological characteristics of yolk sac-derived teratomas were studied in C3H and C57Bl mice and in R and BN rats. The yolk sacs were pulled outside the uterine horns during fetectomy (Fe-x) at varying times during gestation, and they were fixed and examined 2 days later. Mouse yolk sacs examined 2 days after Fe-x on day 11 were similar to those observed in utero on the day of Fe-x, whereas those pulled outside the uterus on day 13 and examined on day 15 showed flattened epithelial cells, reduced mesenchymal cell numbers, and thickened basement membranes. Mouse yolk sacs pulled out on day 15 showed only necrotic cells and a very thick basement membrane. After Fe-x, rat yolk sacs were similar in morphology to those observed in the earlier stages of pregnancy in mice. Treatment of pregnant mice with busulfan (BS: 3 mg/100 g ip on gestation day 9) nearly eliminated the germ cells from the gonads of the newborn offspring. All untreated and BS-treated mice fetectomized on day 11 of pregnancy developed one to four teratomas per uterine horn. The tumors showed endodermal cysts, gut formation, pancreas, epidermal cysts with skin components such as hair and sebaceous glands, cartilage, bone, and bone marrow. Skeletal muscle, nervous tissue, bronchiolar epithelium, lymphoid tissue, and liver were also seen occasionally. The morphology of the tumors varied with the time of Fe-x. The tumors observed in rats were similar to those observed in mice. The data indicate that the capacity of the visceral yolk sac to differentiate into various adult tissues is common to most species of rodents and that benign teratomas develop from the fetal membranes and not from germ cells or embryonal cells. (14 refs)

79-2399 Hematopoietic Stem-Cell Seeding of a Cellular Matrix: A Principle of Initiation and Regeneration of Hematopoiesis. (Eng) Flidner, T. M. (Abteilung für Klinische Physiologie, Universität Ulm, Ulm, W. Germany); Calvo, W. *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 757-773; 1978.

Evidence is presented for the hypothesis that efficient hematopoietic cell differentiation and blood cell production require an interaction between a stem cell population and a suitable cellular matrix. Studies of the human embryo indicated that bone marrow development takes 15 wk. In each skeletal part, the sequence of events leading to the establishment first of a matrix and secondly of hematopoietic parenchyma was the same. During a 1- to 2-wk period, the bone

marrow consisted of a matrix but not of hematopoietic parenchyma. Stem cell seeding of this matrix appeared to be a process having several stages. Electron microscope studies of the bone marrow of dogs that had been rendered aplastic by lethal whole-body x-irradiation indicated that circulating stem cells leave the blood and enter the extravascular space to initiate colonization of the marrow. The kinetic response of matrix cells to the seeding of normal and leukemic stem cells was studied in rats. Under normal circumstances, the cellular matrix had a slow renewal rate that could be measured by the (³H)-thymidine labeling method. The renewal rate was not altered by emigration or immigration of stem cells. The mechanical destruction of parts of the cellular matrix, however, resulted in the proliferation of the remaining cells to restore the matrix to its original size. The immigration of leukemic stem cells destroyed the endothelial and reticular matrix of effective hematopoiesis, and apparently inhibited the regeneration of the matrix and the replication of normal hematopoietic stem cells. (34 refs)

79-2400 Cellular and Architectural Factors Influencing the Proliferation of Hematopoietic Stem Cells.

(Eng) Lord, B. I. (Paterson Labs., Christie Hosp. and Holt Radium Inst., Withington, Manchester M20 9BX, England). *Cold Spring Harbor Conf Cell Proliferation* Vol. 5(Book B), 994 pp.; 775-788; 1978.

The organization of stem cells within the bone marrow spaces was examined, and the relationship between bone and the proliferation of stem cells was studied. Marrow from the cylindrical part of the mouse femoral shaft was fractionated into axial and marginal zones of varying sizes, and the cell populations obtained were assayed for spleen colony-forming cells (CFU-S) and for committed granulocyte precursor cells (CFU-C). CFU-S levels were considerably higher (45/10⁵ cells) in the vicinity of the bone surfaces than in the center of the bone (15/10⁵ cells). CFU-C proliferated rapidly in all regions of the marrow, but CFU-S proliferated in the vicinity of the bone but not in the center. Only 6% of bone marrow CFU-S were killed by a single in vivo dose of 1 mCi (³H)-thymidine given 30 min earlier, compared with 60% of bone CFU-S. At 5 days, <10% of bone-derived CFU-S and 60% of marrow-derived CFU-S survived. One fraction (fraction IV) of normal bone marrow extracts specifically inhibited the proliferation of CFU-S. One of the fractions from regenerating bone marrow (RBME-III) stimulated resting CFU-S from normal bone marrow, increasing the proportion in the S phase of DNA synthesis from 9% to 37%. This property was not shared by the corresponding fraction from normal bone marrow, but fraction III from normal bone stimulated CFU-S proliferation in the same way as did RBME-III. It is suggested that the proliferation stimulatory factor found in bone and regenerating bone marrow and the proliferation inhibitory factor found in normal bone marrow act competitively to adjust the level of CFU-S proliferation to suit the animals' requirements. (28 refs)

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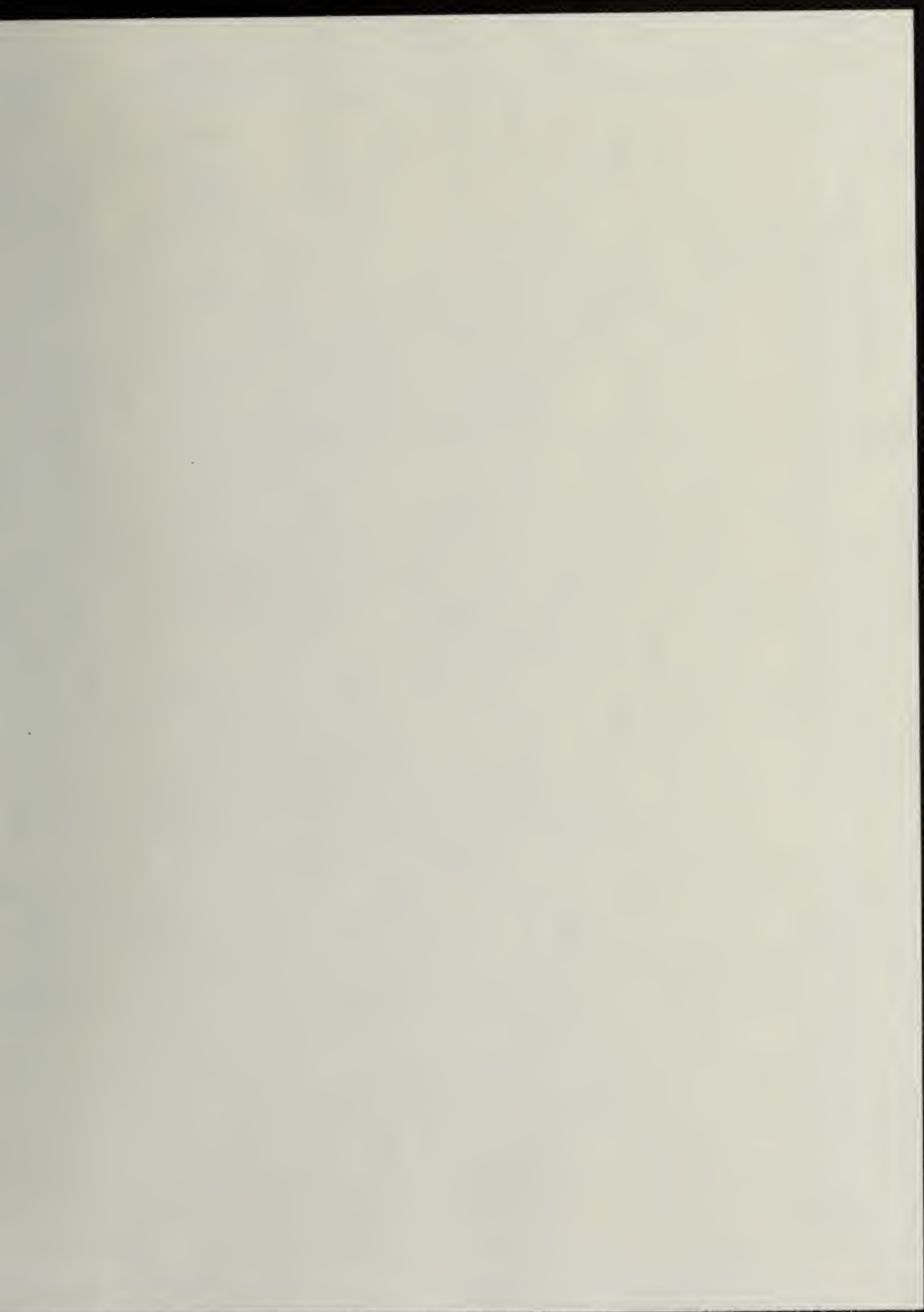
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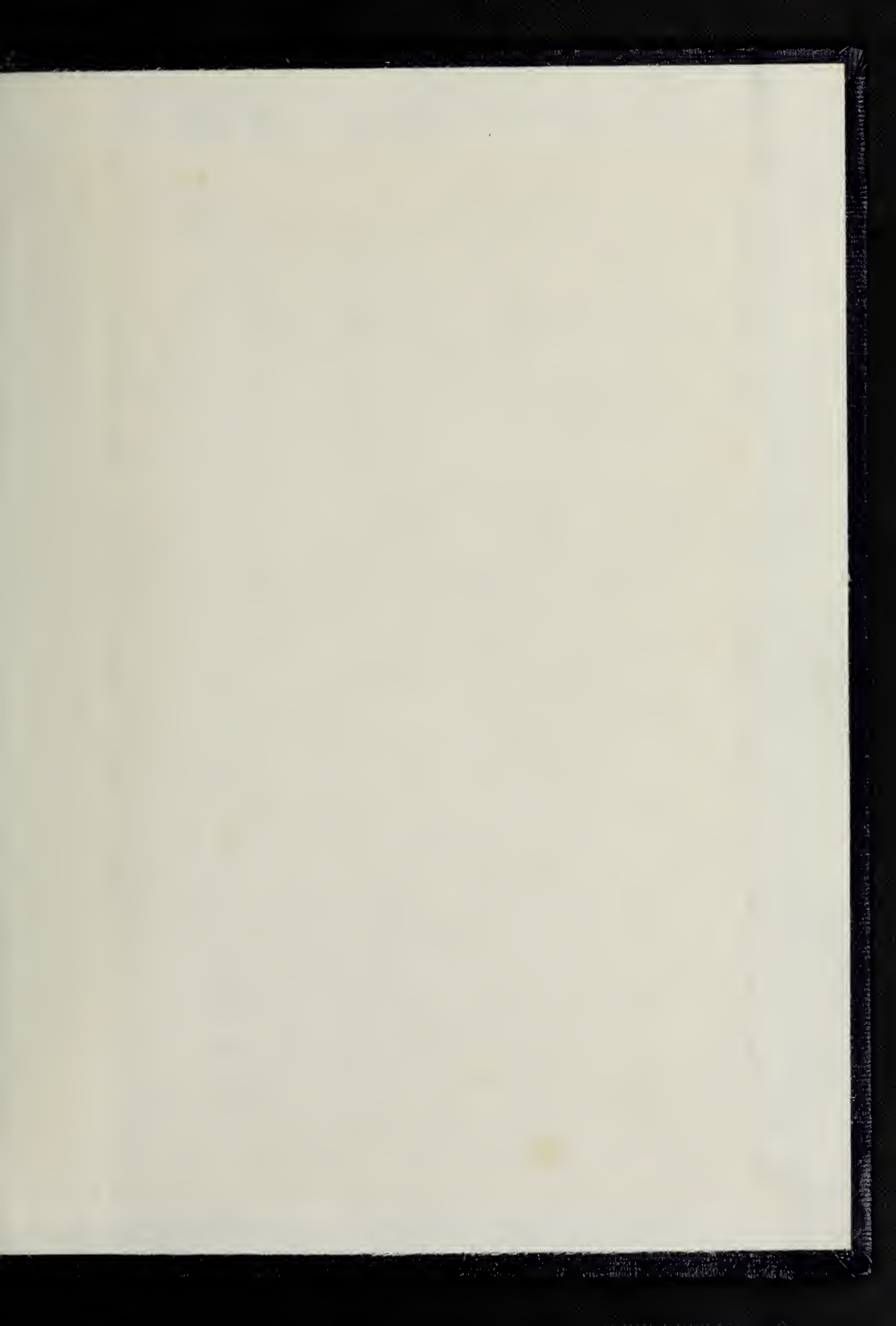
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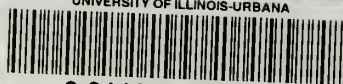
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